IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

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SANOFI-AVENTIS U.S. LLC, AVENTIS PHARMA S.A. and SANOFI

SANOFI-AVENTIS U.S. LLC, AVENTIS PHARMA S.A. and SANOFI Plaintiffs, v. APOTEX CORP. and APOTEX INC. Defendants.	C.A. No.: _____ ***Electronically Filed***

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiffs Sanofi-Aventis U.S. LLC (hereinafter "Sanofi U.S."), Aventis Pharma S.A. (hereinafter "Aventis") and Sanofi (collectively, "Plaintiffs") for their Complaint against defendants Apotex Corp. and Apotex Inc. (collectively "Defendants"), hereby allege as follows:

THE PARTIES

1. Plaintiff Sanofi U.S. is a U.S. subsidiary of Sanofi and is a company organized and existing under the laws of the State of Delaware, having commercial headquarters at 55 Corporate Drive, Bridgewater, New Jersey 08807.

2. Plaintiff Aventis is a corporation organized and existing under the laws of France, having its principal place of business at 20 avenue Raymond Aron, 92160 Antony, France.

3. Plaintiff Sanofi is a corporation organized and existing under the laws of France, having its principal place of business at 54 rue La Boétie, 75008 Paris, France.

4. Plaintiff Sanofi is a global research-driven pharmaceutical company that discovers, develops, manufactures and markets a broad range of innovative products to improve human and animal health.

5. On information and belief, Apotex Corp. is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at 2400 North Commerce Parkway, Suite 400, Weston, Florida 33326.

6. On information and belief, Apotex Inc. is a corporation organized and existing under the laws of Canada, having its principal place of business at 150 Signet Drive, Toronto, Ontario, Canada M9L IT9.

7. On information and belief, Apotex Corp. is a wholly-owned subsidiary of Apotex Inc.

8. On information and belief, Apotex Inc. assembled and caused to be filed with the United States Food and Drug Administration ("FDA"), pursuant to 21 U.S.C. § 355(j) (Section 505(j) of the Federal Food, Drug and Cosmetic Act), Abbreviated New Drug

Application ("ANDA") No. 207736 (hereinafter "the Apotex ANDA") concerning a proposed drug product, Cabazitaxel Injection, 60 mg/1.5 mL ("Apotex's Proposed ANDA Product").

JURISDICTION AND VENUE

9. This action arises under the patent laws of the United States of America. This Court has jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331 and 1338(a).

10. This Court has personal jurisdiction over Apotex Corp. On information and belief, Apotex Corp. directly or through its subsidiaries, affiliates and agents develops, formulates, manufactures, markets, imports and sells pharmaceutical products, including generic drug products, which are copies of products invented and developed by innovator pharmaceutical companies, throughout the United States, including in this Judicial District. On information and belief, Apotex Corp. holds an active wholesale drug license for the State of New Jersey under License No. 5003192.

11. On information and belief, Apotex Corp. is in the business of manufacturing, marketing, importing and selling pharmaceutical drug products, including generic drug products. On information and belief, Apotex Corp. "has successfully secured FDA approval for over 230 ANDAs" and "boast[s] over a billion dollars in sales—and a new ranking in the top 10 generic pharmaceutical companies according to recent IMS HEALTH data." *Apotex Corp: A Global Leader Focused on Excellence*, Pharmacy Times available at http://www.pharmacytimes.com/publications/supplement/2013/Generic-Supplement-2013/Apotex-Corp-A-Global-Leader-Focused-on-Excellence. (last visited January 6, 2015).

12. On information and belief, Apotex Corp. has affiliations with the State of New Jersey that are pervasive, continuous, and systematic. On information and belief, Apotex

Corp. engages in direct marketing, distribution, and/or sale of generic pharmaceutical drugs within the State of New Jersey and to the residents of the State of New Jersey.

13. On information and belief, Apotex Corp. regularly conducts and/or solicits business in the State of New Jersey, engages in other persistent courses of conduct in the State of New Jersey, and/or derives substantial revenue from services or things used or consumed in the State of New Jersey.

14. On information and belief, Apotex Corp. has previously submitted to the jurisdiction of this Court and have availed themselves of the legal protections of the State of New Jersey, having asserted counterclaims in this jurisdiction, including in the matters of *Novartis Pharmaceuticals Corporation v. Apotex Inc. et al.*, Civil Action No. 2:12-cv-05574 (JLL)(MAH), D.I. 12 at 2-3, 10-12 (D.N.J. Feb. 11, 2013); *Otsuka Pharmaceutical Co., Ltd. v. Apotex Corp. et al.*, Civil Action No. 3:12-cv-05645 (MLC) (LHG), D.I. 27 at 3-5, 15-20 (D.N.J. Dec. 11, 2012); *Actelion Pharmaceuticals Ltd. et al. v. Apotex Inc. et al.*, Civil Action No. 1:12-cv-05743 (NLH)(AMD), D.I. 24 at 13-33 (D.N.J. Nov. 27, 2012); and *Hoffman-La Roche, Inc. v. Apotex Inc. et al.*, Civil Action No. 2:10-cv-06241 (SRC)(MAS), D.I. 14 at 3-4, 20-24 (D.N.J. Jan. 12, 2011).

15. On information and belief, upon approval of the Apotex ANDA, Apotex Corp. and/or its subsidiaries, affiliates or agents will market, sell and/or distribute Apotex's Proposed ANDA Product throughout the United States, including in this Judicial District, and will derive substantial revenue therefrom.

16. On information and belief, upon approval of the Apotex ANDA, Apotex Corp. and/or its subsidiaries, affiliates or agents will place Apotex's Proposed ANDA Product

into the stream of commerce with the reasonable expectation or knowledge and the intent that such product will ultimately be purchased and used by consumers in this Judicial District.

17. This Court has personal jurisdiction over Apotex Inc. On information and belief, Apotex Inc. directly or through its subsidiaries, affiliates and agents develops, formulates, manufactures, markets, imports and sells pharmaceutical products, including generic drug products, which are copies of products invented and developed by innovator pharmaceutical companies, throughout the United States, including in this Judicial District. On information and belief, Apotex Inc. is in the business of manufacturing, marketing, importing and selling pharmaceutical drug products, including generic drug products.

18. On information and belief, Apotex Inc. has affiliations with the State of New Jersey that are pervasive, continuous, and systematic. On information and belief, Apotex Inc. engages in direct marketing, distribution, and/or sale of generic pharmaceutical drugs within the State of New Jersey and to the residents of the State of New Jersey.

19. On information and belief, Apotex Inc. regularly conducts and/or solicits business in the State of New Jersey, engages in other persistent courses of conduct in the State of New Jersey, and/or derives substantial revenue from services or things used or consumed in the State of New Jersey.

20. On information and belief, Apotex Inc. has previously submitted to the jurisdiction of this Court and have availed themselves of the legal protections of the State of New Jersey, having asserted counterclaims in this jurisdiction, including in the matters of *Novartis Pharmaceutical Corporation v. Apotex Inc. et al.*, Civil Action No. 2:12-cv-05574 (JLL)(MAH), D.I. 12 at 2-3, 10-12 (D.N.J. Feb. 11, 2013); *Otsuka Pharmaceutical Co., Ltd. v. Apotex Corp. et al.*, Civil Action No. 3:12-cv-05645 (MLC) (LHG), D.I. 27 at 3-5, 15-20 (D.N.J. Dec. 11, 2012);

Actelion Pharmaceuticals Ltd. et al. v. Apotex Inc. et al., Civil Action No. 1:12-cv-05743 (NLH)(AMD), D.I. 24 at 13-33 (D.N.J. Nov. 27, 2012); and *Hoffman-La Roche, Inc. v. Apotex Inc. et al.*, Civil Action No. 2:10-cv-06241 (SRC)(MAS), D.I. 14 at 3-4, 20-24 (D.N.J. Jan. 12, 2011).

21. Apotex Inc. is also subject to personal jurisdiction in the State of New Jersey because, *inter alia*, Apotex Inc. has committed, aided, abetted, contributed to, and/or participated in the commission of a tortious act of patent infringement under 35 U.S.C. § 271(e)(2) that has led and/or will lead to foreseeable harm and injury to Plaintiff Sanofi U.S., having commercial headquarters in the State of New Jersey. Apotex Inc. sent its December 4, 2014 Paragraph IV Notice Letter to Sanofi U.S.'s commercial headquarters at 55 Corporate Drive, Bridgewater, New Jersey 08807. Plaintiffs's cause of action arose from Apotex Inc.'s contact with Sanofi U.S. in Bridgewater, New Jersey. Apotex Inc. states that it intends to engage in the commercial manufacture, use, and/or sale of Apotex Inc.'s Proposed ANDA Product before the expiration of U.S Patent Nos. 5,847,170 ("'170 patent") and 7,241,907 ("'907 patent") throughout the United States, including in this Judicial District.

22. In the alternative, Apotex Inc. is subject to jurisdiction in the United States under the principles of general jurisdiction, and specially in the State of New Jersey pursuant to Fed. R. Civ. P. 4(k)(2). Apotex Inc. has contacts with the United States by, *inter alia*, its having filed an ANDA with the FDA.

23. On information and belief, upon approval of the Apotex ANDA, Apotex Inc. and/or its subsidiaries, affiliates or agents will market, sell and/or distribute Apotex's Proposed ANDA Product throughout the United States, including in this Judicial District, and will derive substantial revenue therefrom.

24. On information and belief, upon approval of the Apotex ANDA, Apotex Inc. and/or its subsidiaries, affiliates or agents will place Apotex's Proposed ANDA Product into the stream of commerce with the reasonable expectation or knowledge and the intent that such product will ultimately be purchased and used by consumers in this Judicial District.

25. Venue is proper in this Court at least pursuant to 28 U.S.C. §§ 1391(b), (c), and/or (d), and 1400(b).

THE PATENTS-IN-SUIT

26. Sanofi U.S. holds approved New Drug Application ("NDA") No. 201023 for cabazitaxel injection, 60 mg/ 1.5 mL (40 mg/mL), which is prescribed and sold in the United States under the trademark JEVTANA® KIT (hereinafter "JEVTANA®"). The U.S. Food and Drug Administration ("FDA") approved NDA No. 201023 on June 17, 2010. JEVTANA® is approved for use in combination with prednisone for the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen.

27. United States Patent No. 5,847,170 (the "'170 patent," copy attached as Exhibit A) is entitled "Taxoids, Their Preparation And Pharmaceutical Compositions Containing Them" and was duly and legally issued by the United States Patent and Trademark Office ("USPTO") on December 8, 1998. The '170 patent claims, *inter alia*, cabazitaxel and pharmaceutical compositions containing cabazitaxel. The '170 patent is listed in the FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book") for JEVTANA® (NDA No. 201023).

28. The '170 patent is owned by Aventis.

29. United States Patent No. 7,241,907 (the "'907 patent," copy attached as Exhibit B) is entitled "Acetone Solvate of Dimethoxy Docetaxel and its Process of Preparation" and was duly and legally issued by the United States Patent and Trademark Office ("USPTO") on July 10, 2007. The '907 patent claims, *inter alia*, an acetone solvate of cabazitaxel. The '907 patent is listed in the FDA's Orange Book for JEVTANA® (NDA No. 201023).

30. The '907 patent is owned by Aventis.

CLAIMS FOR RELIEF – PATENT INFRINGEMENT

31. On information and belief, Apotex Inc. submitted the Apotex ANDA to the FDA seeking approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Apotex's Proposed ANDA Product.

32. On information and belief, the Apotex ANDA seeks FDA approval of Apotex's Proposed ANDA Product for use in combination with prednisone for the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen.

33. On information and belief, Apotex Inc. actively collaborated with Apotex Corp. and/or participated in and/or directed activities related to the submission of the Apotex ANDA and the development of Apotex's Proposed ANDA Product, was actively involved in preparing the ANDA, and/or intends to directly benefit from and has a financial stake in the approval of the ANDA. On information and belief, upon approval of the Apotex ANDA, Apotex Inc. will be involved in the manufacture, distribution, and/or marketing of Apotex's Proposed ANDA Product.

34. On information and belief, Apotex Corp. actively collaborated with Apotex Inc. and/or participated in and/or directed activities related to the submission of the

Apotex ANDA and the development of Apotex's Proposed ANDA Product, was actively involved in preparing the ANDA, and/or intends to directly benefit from and has a financial stake in the approval of the ANDA. On information and belief, upon approval of the Apotex ANDA, Apotex Corp. will be involved in the manufacture, distribution, and/or marketing of Apotex's Proposed ANDA Product.

35. By letter dated December 4, 2014 (the "December 4 Letter"), and pursuant to 21 U.S.C. § 355(j)(2)(B)(ii) and 21 C.F.R. §314.95, Apotex Inc. notified Plaintiffs that it had submitted to the FDA the Apotex ANDA, seeking approval to engage in the commercial manufacture, use, or sale of Apotex's Proposed ANDA Product before the expiration of the '170 patent and the '907 patent. The December 4 Letter was received by Plaintiffs on December 5, 2014.

36. In its December 4 Letter, Apotex Inc. notified Plaintiffs, as part of the Apotex ANDA, it had filed a certification of the type described in 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (a "Paragraph IV Certification") with respect to the '170 patent and the '907 patent. On information and belief, Apotex Inc. certified that, the '170 patent and the '907 patent are invalid, unenforceable and/or will not be infringed by the manufacture, use or sale of Apotex's Proposed ANDA Product.

37. The Apotex ANDA refers to and relies upon the Sanofi U.S.'s NDA No. 201023 for JEVTANA®.

38. In the December 4 Letter, Apotex offered confidential access to portions of the Apotex ANDA on terms and conditions set forth in paragraph 2 of the December 4 Letter ("Apotex Offer"). Apotex requested that Plaintiffs accept the Apotex Offer before receiving access to any portion of the Apotex ANDA. The Apotex Offer contained unreasonable

restrictions that would apply under a protective order. For example, the Apotex Offer required that Plaintiffs' outside counsel do not engage, formally or informally, in any patent prosecution or any FDA counseling, litigation or other work before or involving the FDA on behalf of Plaintiffs.

39. Under 21 U.S.C. § 355(j)(5)(C)(i)(III), an "offer of confidential access shall contain such restrictions . . . on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information."

40. Since rejecting the Apotex Offer, Plaintiffs attempted to negotiate with Apotex to obtain a copy of excerpts of the Apotex ANDA under restrictions "as would apply had a protective order been issued." Those negotiations were unsuccessful. For example, Apotex's final proposal continued to unreasonably impose patent prosecution and FDA restrictions on Plaintiffs' outside counsel.

41. Plaintiffs are not aware of any other means of obtaining information regarding Apotex's Proposed ANDA Product within the 45-day statutory period. Without such information, Plaintiffs will use the judicial process and the aid of discovery to obtain, under appropriate judicial safeguards such information as is required to confirm its allegations of infringement and to present to the Court evidence that Apotex's Proposed ANDA Product falls within the scope of one or more claims of the '170 and '907 patents.

COUNT I

INFRINGEMENT OF U.S. PATENT NO. 5,847,170

42. Plaintiff repeats and realleges paragraphs 1 through 41 above as if fully set forth herein.

43. By submitting the Apotex ANDA under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use or sale of Apotex's Proposed ANDA Product throughout the United States prior to the expiration of the '170 patent, Defendants committed an act of infringement of the '170 patent under 35 U.S.C. § 271(e)(2). On information and belief, Defendants were aware of the '170 patent at the time the Apotex ANDA was submitted.

44. If Defendants commercially make, use, offer to sell, or sell Apotex's Proposed ANDA Product within the United States, or import Apotex's Proposed ANDA Product into the United States, or induce or contribute to any such conduct during the term of the '170 patent, they would further infringe the '170 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

45. Plaintiffs will be irreparably harmed if Defendants are not enjoined from infringing the '170 patent. Plaintiffs do not have an adequate remedy at law.

46. Apotex Inc.'s certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) against the '170 patent was wholly unjustified, and thus this case is exceptional under 35 U.S.C. § 285.

COUNT II

INFRINGEMENT OF U.S. PATENT NO. 7,241,907

47. Plaintiffs repeat and reallege paragraphs 1 through 46 above as if fully set forth herein.

48. By submitting the Apotex ANDA under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use or sale of Apotex's Proposed ANDA Product throughout the United States prior to the expiration of the '907 patent, Defendants committed an act of infringement of the '907 patent under 35 U.S.C. § 271(e)(2). On

information and belief, Defendants were aware of the '907 patent at the time the Apotex ANDA was submitted.

49. If Defendants commercially make, use, offer to sell, or sell Apotex's Proposed ANDA Product within the United States, or import Apotex's Proposed ANDA Product into the United States, or induce or contribute to any such conduct during the term of the '907 patent, it would further infringe the '907 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

50. Plaintiffs will be irreparably harmed if Defendants are not enjoined from infringing the '907 patent. Plaintiffs do not have an adequate remedy at law.

51. Apotex Inc.'s certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) against the '907 patent was wholly unjustified, and thus this case is exceptional under 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request the following relief:

A. A judgment that Defendants have infringed one or more claims of the '170 patent by filing ANDA No. 207736 relating to Apotex's Proposed ANDA Product before the expiration of the '170 patent;

B. A judgment that the manufacture, use, offer for sale, sale and/or importation of Apotex's Proposed ANDA Product will infringe the '170 patent;

C. A judgment declaring that the '170 patent remains valid and enforceable;

D. A permanent injunction restraining and enjoining Defendants, and their officers, agents, attorneys and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of Apotex's Proposed ANDA Product until the expiration of

the ’170 patent or any later date of exclusivity to which Plaintiffs and/or the ’170 patent are or become entitled to;

E. An order that the effective date of any approval of Apotex’s ANDA No. 207736 relating to Apotex’s Proposed ANDA Product under Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)) shall be a date that is not earlier than the expiration date of the ’170 patent or any later date of exclusivity to which Plaintiffs and/or the ’170 patent are or become entitled;

F. A judgment that Defendants have infringed one or more claims of the ’907 patent by filing ANDA No. 207736 relating to Apotex’s Proposed ANDA Product before the expiration of the ’907 patent;

G. A judgment that the manufacture, use, offer for sale, sale and/or importation of Apotex’s Proposed ANDA Product will infringe the ’907 patent;

H. A judgment declaring that the ’907 patent remains valid and enforceable;

I. A permanent injunction restraining and enjoining Defendants, and their officers, agents, attorneys and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of Apotex’s Proposed ANDA Product until the expiration of the ’907 patent or any later date of exclusivity to which Plaintiffs and/or the ’907 patent are or become entitled to;

J. An order that the effective date of any approval of Apotex’s ANDA No. 207736 relating to Apotex’s Proposed ANDA Product under Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)) shall be a date that is not earlier than the expiration

date of the ’907 patent or any later date of exclusivity to which Plaintiffs and/or the ’907 patent are or become entitled;

K. A declaration that this case is “exceptional” within the meaning of 35 U.S.C. § 285 and an award of reasonable attorney fees, costs, expenses, and disbursements of this action; and

L. Such other and further relief as the Court may deem just and proper.

January 14, 2015

CONNELL FOLEY LLP

By: *s/Liza M. Walsh*

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RULE 11.2 CERTIFICATION

I, Liza M. Walsh, admitted to the bars of the State of New Jersey and this Court, and a Partner in the law firm of Connell Foley LLP representing Plaintiffs Sanofi-Aventis U.S. LLC, Aventis Pharma S.A. and Sanofi in the above-captioned matter, hereby certify pursuant to L. Civ. R. 11.2 that the matter in controversy in this action is related to the following actions that are pending before the District Court for the District of New Jersey: *Sanofi-Aventis U.S. LLC et al. v. Fresenius Kabi USA, LLC*, C. A. No. 14-7869 (MAS)(LHG); *Sanofi-Aventis U.S. LLC et al. v. Accord Healthcare, Inc.*, C. A. No. 14-8079 (MAS)(LHG); *Sanofi-Aventis U.S. LLC et al. v. BPI Labs, LLC et al.*, C. A. No. 14-8081 (MAS)(LHG); *Sanofi-Aventis U.S. LLC et al. v. Fresenius Kabi USA, LLC*, C. A. No. 14-8082 (MAS)(LHG); the following actions pending before the District Court for the District of Delaware: *Sanofi-Aventis U.S. LLC et al. v. Fresenius Kabi USA, LLC*, C. A. No. 14-1496 (LPS); and *Sanofi-Aventis U.S. LLC et al. v. Fresenius Kabi USA, LLC*, C. A. No. 14-1533 (LPS); one pending litigation in the District Court for the Middle District of Florida: *Sanofi-Aventis U.S. LLC et al. v. BPI Labs, LLC et al.*, C. A. No. 14-3233 (EAK)(TGW); and one pending litigation in the District Court for the Middle District of North Carolina: *Sanofi-Aventis U.S. LLC et al. v. Accord Healthcare, Inc.*, C. A. No. 15-0018 (NCT)(LPA).

I certify under penalty of perjury that the foregoing is true and correct.

January 14, 2015

CONNELL FOLEY LLP

By: *s/Liza M. Walsh*

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RULE 201.1 CERTIFICATION

We hereby certify that the above-captioned matter is not subject to compulsory arbitration in that the plaintiffs seek, inter alia, injunctive relief.

January 14, 2015

CONNELL FOLEY LLP

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EXHIBIT A

US005847170A

United States Patent [19]

Bouchard et al.

[11] **Patent Number: 5,847,170**

[45] **Date of Patent: Dec. 8, 1998**

[54] **TAXOIDS, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM**

[75] Inventors: **Hervé Bouchard**, Ivry-sur-Seine; **Jean-Dominique Bourzat**, Vincennes; **Alain Commerçon**, Vitry-sur-Seine, all of France

[73] Assignee: **Rhône-Poulenc Rorer, S.A.**, Antony Cedex, France

[21] Appl. No.: **622,011**

[22] Filed: **Mar. 26, 1996**

Related U.S. Application Data

[60] Provisional application No. 60/010,144, Jan. 17, 1996.

[30] **Foreign Application Priority Data**

Mar. 27, 1995 [FR] France 95 03545
Dec. 22, 1995 [FR] France 95 15381

[51] **Int. Cl.**[6] **C07D 305/14**
[52] **U.S. Cl.** **549/510**; 549/511
[58] **Field of Search** 549/510, 511

[56] **References Cited**

U.S. PATENT DOCUMENTS

5,229,526	7/1993	Holton et al.	549/213
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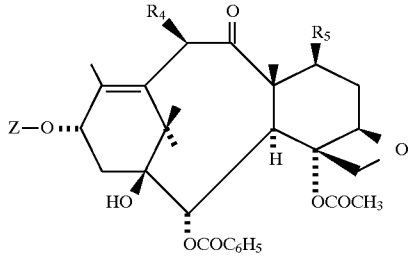
J. Kant et al., "A Chemoselective Approach to Functionalize the C–10 Position of 10–Deacetylbaccatin III. Synthesis and Biological Properties of Novel C–10 Taxol Analogues", Tetrahedron Letters, vol. 35, No. 31, pp. 5543–5546, 1994.

Primary Examiner—Ba K. Trinh
Attorney, Agent, or Firm—Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.

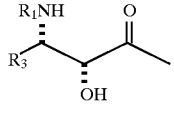
[57] **ABSTRACT**

New taxoids of general formula (I):



(I)

their preparation and pharmaceutical compositions containing them, and the new products of general formula (I) in which Z represents a radical of general formula (II):



(II)

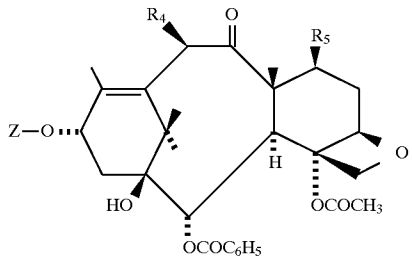
display noteworthy antitumour and antileukaemic properties.

22 Claims, No Drawings

TAXOIDS, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

This application claims the priority of U.S. provisional application 60/010,144 filed Jan. 17, 1996.

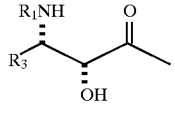
The present invention relates to new taxoids of general formula (I)



(I)

in which:

Z represents a hydrogen atom or a radical of general formula (II):



(II)

in which:

R_1 represents

a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms and trifluoromethyl radicals,

a thenoyl or furoyl radical or

a radical R_2—O—CO— in which R_2 represents:

an alkyl radical containing 1 to 8 carbon atoms,

an alkenyl radical containing 2 to 8 carbon atoms,

an alkynyl radical containing 3 to 8 carbon atoms,

a cycloalkyl radical containing 3 to 6 carbon atoms,

a cycloalkenyl radical containing 4 to 6 carbon atoms or

a bicycloalkyl radical containing 7 to 10 carbon atoms,

these radicals being optionally substituted with one or more substituents selected from halogen atoms, hydroxyl radicals, alkoxy radicals containing 1 to 4 carbon atoms, dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms, piperidino radicals, morpholino radicals, 1-piperazinyl radicals, said piperazinyl radicals being optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms, cycloalkyl radicals containing 3 to 6 carbon atoms, cycloalkenyl radicals containing 4 to 6 carbon atoms, phenyl radicals, said phenyl radicals being optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, and alkoxy radicals containing 1 to 4 carbon atoms, cyano radicals, carboxyl radicals and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, and alkoxy radicals containing 1 to 4 carbon atoms,

a 5-membered aromatic heterocyclic radical preferably selected from furyl and thienyl radicals,

or a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

R_3 represents

an unbranched or branched alkyl radical containing 1 to 8 carbon atoms,

an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms,

an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms,

a cycloalkyl radical containing 3 to 6 carbon atoms,

a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals,

or a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

with the understanding that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

R_4 represents

an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

an alkenyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain,

an alkynyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain,

a cycloalkyloxy radical containing 3 to 6 carbon atoms or

a cycloalkenyloxy radical containing 4 to 6 carbon atoms,

these radicals being optionally substituted with one or more substituents selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 1 to 4 carbon atoms, a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical and a N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms, or both alkyl portions, together with the nitrogen atom to which they are linked, form a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, said saturated 5- or 6-membered heterocyclic radical optionally being substituted with a substituent selected from an alkyl radical containing 1 to 4 carbon atoms, a phenyl radical, and a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms,

R_5 represents

an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

an alkenyloxy radical containing 3 to 6 carbon atoms,

an alkynyloxy radical containing 3 to 6 carbon atoms,

a cycloalkyloxy radical containing 3 to 6 carbon atoms or

a cycloalkenyloxy radical containing 3 to 6 carbon atoms,

these radicals being optionally substituted with at least one substituent selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 2 to 4 carbon atoms, a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical, and a N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms or, with the nitrogen atom to which it is linked, forms a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, optionally substituted with a substituent selected from an alkyl radical containing 1 to 4 carbon atoms, a phenyl radical and a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms.

Preferably, the aryl radicals which can be represented by R_3 are phenyl or α- or β-naphthyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms (fluorine, chlorine, bromine, iodine) alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, on the understanding that the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, that the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms and that the aryl radicals are phenyl or α- or β-naphthyl radicals.

Preferably, the heterocyclic radicals which can be represented by R_3 are 5-membered aromatic heterocyclic radicals containing one or more identical or different atoms selected from nitrogen, oxygen and sulphur atoms, optionally substituted with one or more identical or different substituents selected from halogen atoms (fluorine, chlorine, bromine, iodine), alkyl radicals containing 1 to 4 carbon atoms, aryl radicals containing 6 or 10 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, aryloxy radicals containing 6 or 10 carbon atoms, amino radicals, alkylamino radicals containing 1 to 4 carbon atoms, dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms, acylamino radicals in which the acyl portion contains 1 to 4 carbon atoms, alkoxycarbonylamino radicals containing 1 to 4 carbon atoms, acyl radicals containing 1 to 4 carbon atoms, arylcarbonyl radicals in which the aryl portion contains 6 or 10 carbon atoms, cyano radicals, carboxyl radicals, carbamoyl radicals, alkylcarbamoyl radicals in which the alkyl portion contains 1 to 4 carbon atoms, dialkylcarbamoyl radicals in which each alkyl portion contains 1 to 4 carbon atoms, and alkoxycarbonyl radicals in which the alkoxy portion contains 1 to 4 carbon atoms.

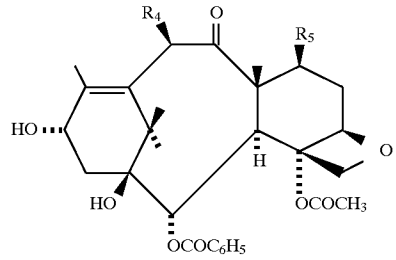
Preferably, the radicals R_4 and R_5, which may be identical or different, represent unbranched or branched alkoxy radicals containing 1 to 6 carbon atoms, optionally substituted with a methoxy, ethoxy, ethylthio, carboxyl, methoxycarbonyl, ethoxycarbonyl, cyano, carbamoyl, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-pyrrolidinocarbonyl or N-piperidinocarbonyl radical.

More particularly, the present invention relates to the products of general formula (I) in which Z represents a hydrogen atom or a radical of general formula (II) in which R_1 represents a benzoyl radical or a radical R_2—O—CO— in which R_2 represents a tert-butyl radical and R_3 represents an alkyl radical containing 1 to 6 carbon atoms, an alkenyl radical containing 2 to 6 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl radical optionally substituted with one or more identical or different atoms or radicals selected from from halogen atoms (fluorine, chlorine), alkyl (methyl), alkoxy (methoxy), dialkylamino (dimethylamino), acylamino (acetylamino), alkoxycarbonylamino (tert-butoxycarbonylamino), trifluoromethyl, a 2-furyl radical, a 3-furyl radical, a 2-thienyl radical, a 3-thienyl radical, a 2-thiazolyl radical, a 4-thiazolyl radical, and a 5-thiazolyl radical, and R_4 and R_5, which may be identical or different, each represent an unbranched or branched alkoxy radical containing 1 to 6 carbon atoms.

Still more particularly, the present invention relates to the products of general formula (I) in which Z represents a hydrogen atom or a radical of general formula (II) in which R_1 represents a benzoyl radical or a radical R_2—O—CO— in which R_2 represents a tert-butyl radical and R_3 represents an isobutyl, isobutenyl, butenyl, cyclohexyl, phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl or 5-thiazolyl radical, and R_4 and R_5, which may be identical or different, each represent a methoxy, ethoxy or propoxy radical.

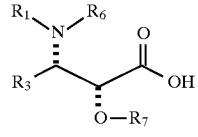
The products of general formula (I) in which Z represents a radical of general formula (II) display noteworthy antitumour and antileukaemic properties.

According to the present invention, the new products of general formula (I) in which Z represents a radical of general formula (II) may be obtained by esterification of a product of general formula (III):



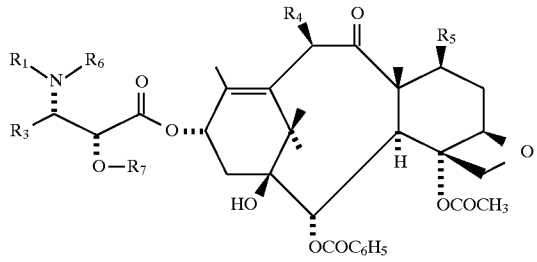
(III)

in which R_4 and R_5 are defined as above, by means of an acid of general formula (IV):



(IV)

in which R_1 and R_3 are defined as above, and either R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, or R_6 and R_7 together form a saturated 5- or 6-membered heterocycle, or by means of a derivative of this acid, to obtain an ester of general formula (V):



(V)

in which R_1, R_3, R_4, R_5, R_6 and R_7 are defined as above, followed by replacement of the protective groups represented by R_7 and/or R_6 and R_7 by hydrogen atoms.

The esterification by means of an acid of general formula (IV) may be performed in the presence of a condensing agent (carbodiimide, reactive carbonate) and an activating agent (aminopyridines) in an organic solvent (ether, ester, ketones, nitriles, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons) at a temperature from −10° to 90° C.

The esterification may also be carried out using the acid of general formula (IV) in the form of the symmetrical anhydride, working in the presence of an activating agent (aminopyridines) in an organic solvent (ethers, esters, ketones, nitrites, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons) at a temperature of from 0° to 90° C.

The esterification may also be carried out using the acid of general formula (IV) in halide form or in the form of a mixed anhydride with an aliphatic or aromatic acid, optionally prepared in situ, in the presence of a base (tertiary aliphatic amine), working in an organic solvent (ethers, esters, ketones, nitriles, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons) at a temperature of from 0° to 80° C.

Preferably, R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, or alternatively R_6 and R_7 together form a saturated 5- or 6-membered heterocycle.

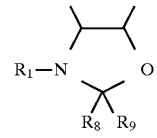
When R_6 represents a hydrogen atom, R_7 preferably represents a methoxymethyl, 1-ethoxyethyl, benzyloxymethyl, trimethylsilyl, triethylsilyl, β-trimethylsilylethoxymethyl, benzyloxycarbonyl or tetrahydropyranyl radical.

When R_6 and R_7 together form a heterocycle, the latter is preferably an oxazolidine ring optionally monosubstituted or gem-disubstituted at position 2.

Replacement of the protective groups R_7 and/or R_6 and R_7 by hydrogen atoms may be performed, depending on their nature, in the following manner:

1) when R_8 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, replacement of the protective groups by hydrogen atoms is performed by means of an inorganic acid (hydrochloric acid, sulphuric acid, hydrofluoric acid) or organic acid (acetic acid, methanesulphonic acid, trifluoromethanesulphonic acid, p-toluenesulphonic acid) used alone or mixed, working in an organic solvent chosen from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons or nitriles at a temperature of from −10° to 60° C., or by means of a source of fluoride ions such as a hydrofluorine acid/triethylamine complex, or by catalytic hydrogenation,

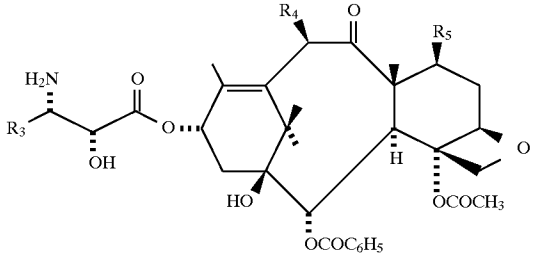
2) when R_6 and R_7 together form a saturated 5- or 6-membered heterocycle, and more especially an oxazolidine ring of general formula (VI):



(VI)

in which R_1 is defined as above and R_6 and R_9, which may be identical or different, represent a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, or an aralkyl radical in which the alkyl portion contains 1 to 4 carbon atoms and the aryl portion preferably represents a phenyl radical optionally substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms, or an aryl radical preferably representing a phenyl radical optionally substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms, or alternatively R_8 represents an alkoxy radical containing 1 to 4 carbon atoms or a trihalomethyl radical such as trichloromethyl or a phenyl radical substituted with a trihalomethyl radical such as trichloromethyl and R_9 represents a hydrogen atom, or alternatively R_8 and R_9, together with the carbon atom to which they are linked, form a 4- to 7-membered ring, replacement of the protective group formed by R_6 and R_7 by hydrogen atoms may be performed, depending on the meanings of R_1, R_8 and R_9, in the following manner:

a) when R_1 represents a tert-butoxycarbonyl radical and R_8 and R_9, which may be identical or different, represent an alkyl radical or an aralkyl (benzyl) or aryl (phenyl) radical, or alternatively R_8 represents a trihalomethyl radical or a phenyl radical substituted with a trihalomethyl radical and R_9 represents a hydrogen atom, or alternatively R_8 and R_9 together form a 4- to 7-membered ring, treatment of the ester of general formula (V) with an inorganic or organic acid, where appropriate in an organic solvent such as an alcohol, yields the product of general formula (VII):



(VII)

in which R_3, R_4 and R_5 are defined as above, which is acylated by means of benzoyl chloride in which the phenyl ring is optionally substituted or by means of thenoyl chloride, of furoyl chloride or of a product of general formula:

$$R_2—O—CO—X \qquad \text{(VIII)}$$

in which R_2 is defined as above and X represents a halogen atom (fluorine, chlorine) or a residue —O—R_2 or —O—CO—O—R_2, to obtain a product of general formula (I) in which Z represents a radical of general formula (II).

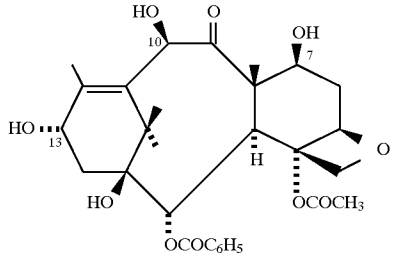
Preferably, the product of general formula (V) is treated with formic acid at a temperature in the region of 20° C. to yield the product of general formula (VII).

Preferably, the acylation of the product of general formula (VII) by means of a benzoyl chloride in which the phenyl radical is optionally substituted or by means of thenoyl chloride, of furoyl chloride or of a product of general formula (VIII) is performed in an inert organic solvent

chosen from esters such as ethyl acetate, isopropyl acetate or n-butyl acetate and halogenated aliphatic hydrocarbons such as dichloromethane or 1,2-dichloroethane, in the presence of an inorganic base such as sodium bicarbonate or an organic base such as triethylamine. The reaction is performed at a temperature of from 0° to 50° C., and preferably at about 20° C.

b) when R_1 represents an optionally substituted benzoyl radical, a thenoyl or furoyl radical or a radical R_2O—CO— in which R_2 is defined as above, R_8 represents a hydrogen atom or an alkoxy radical containing 1 to 4 carbon atoms or a phenyl radical substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms and R_9 represents a hydrogen atom, replacement of the protective group formed by R_6 and R_7 by hydrogen atoms is performed in the presence of an inorganic acid (hydrochloric acid, sulphuric acid) or organic acid (acetic acid, methanesulphonic acid, trifluoromethanesulphonic acid, p-toluenesulphonic acid) used alone or mixed in a stoichiometric or catalytic amount, working in an organic solvent chosen from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons and aromatic hydrocarbons at a temperature of from −10° to 60° C., and preferably from 15° to 30° C.

According to the invention, the products of general formula (III), that is to say the products of general formula (I) in which Z represents a hydrogen atom and R_4 and R_5 are defined as above, may be obtained from 10-deacetylbaccatin III of formula (IX):

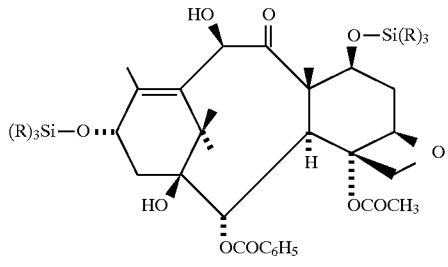


(IX)

It can be especially advantageous to protect the hydroxyl functions at the positions 7 and 13 selectively, for example in the form of a silyl diether which may be obtained by the action of a silyl halide of general formula:

$(R)_3$—Si—Hal (X)

in which the symbols R, which may be identical or different, represent an alkyl radical containing 1 to 6 carbon atoms, optionally substituted with a phenyl radical, or a cycloalkyl radical containing 3 to 6 carbon atoms or a phenyl radical, on 10-deacetylbaccatin III, to obtain a product of general formula (XI):

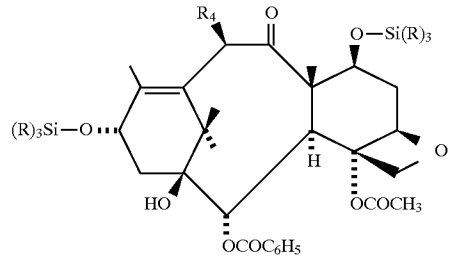


(XI)

in which R is defined as above, followed by the action of a product of general formula:

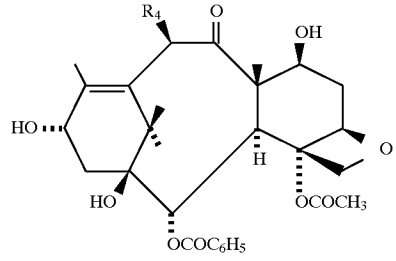
R'_4—X_1 (XII)

in which R'_4 represents a radical such that R'_4—O is identical to R_4 defined as above and X_1 represents a reactive ester residue such as a sulphuric or sulphonic ester residue or a halogen atom, to obtain a product of general formula (XIII):



(XIII)

in which R and R_4 are defined as above, the silyl protective groups of which are replaced by hydrogen atoms to obtain a product of general formula (XIV):



(XIV)

in which R_4 is defined as above, which is etherified selectively at position 7 by the action of a product of general formula:

R'_5—X_2 (XV)

in which R'_5 represents a radical such that R'_5—O is identical to R_5 defined as above and X_2 represents a halogen atom or a reactive ester residue such as a sulphuric or sulphonic ester residue, to give the product of general formula (III).

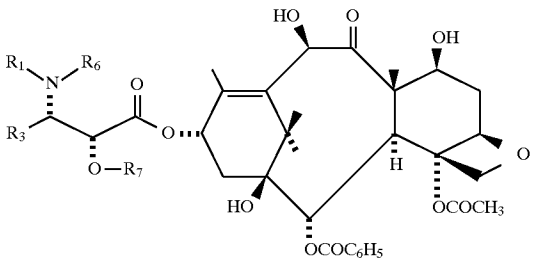
Generally, the action of a silyl derivative of general formula (X) on 10-deacetylbaccatin III is performed in pyridine or triethylamine, where appropriate in the presence of an organic solvent such as an aromatic hydrocarbon, for instance benzene, toluene or xylenes, at a temperature between 0° C. and the refluxing temperature of the reaction mixture.

Generally, the action of a product of general formula (XII) on a product of general formula (XI) is performed, after metalation of the hydroxyl function at position 10 by means of an alkali metal hydride, such as sodium hydride, an alkali metal amide, such as lithium amide, or an alkali metal alkylide, such as butyllithium, working in an organic solvent, such as dimethylformamide or tetrahydrofuran, at a temperature of from 0° to 50° C.

Generally, the replacement of the silyl protective groups of the product of general formula (XIII) by hydrogen atoms is performed by means of an acid such as hydrofluoric acid or trifluoroacetic acid in the presence of a base such as triethylamine or pyridine optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms, the base optionally being combined with an inert organic solvent such as a nitrile, for instance acetonitrile, or a halogenated aliphatic hydrocarbon, such as dichloromethane, at a temperature of from 0° to 80° C.

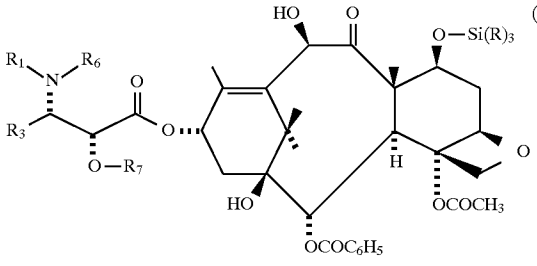
Generally, the action of a product of general formula (XV) on a product of general formula (XIV) is performed under the conditions described above for the action of a product of general formula (XII) on a product of general formula (XI).

According to the invention, the products of general formula (I) in which Z represents a radical of general formula (II), R_4 is defined as above and R_5 is defined as above may be obtained from a product of general formula (XVI):



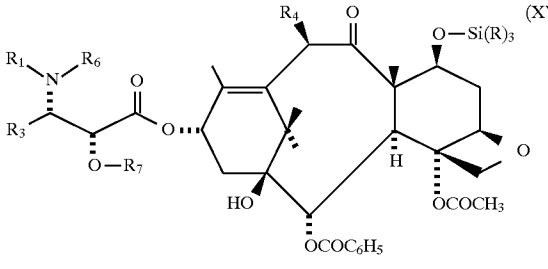
(XVI)

in which R_1, R_3, R_6 and R_7 are defined as above, by silylation at position 7 by means of a product of general formula (X), to obtain a product of general formula (XVII):



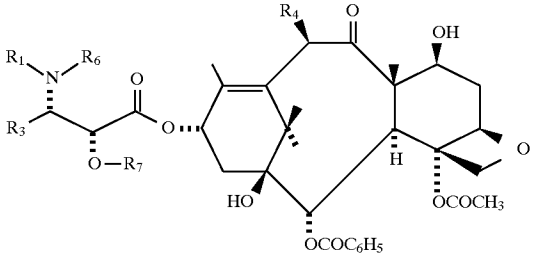
(XVII)

in which R, R_1, R_3, R_6 and R_7 are defined as above, which is functionalized at position 10 by means of a product of general formula (XII) to give a product of general formula (XVIII):



(XVIII)

in which R, R_1, R_3, R_4, R_6 and R_7 are defined as above, the silyl protective group of which is replaced by a hydrogen atom to give a product of general formula (XIX):

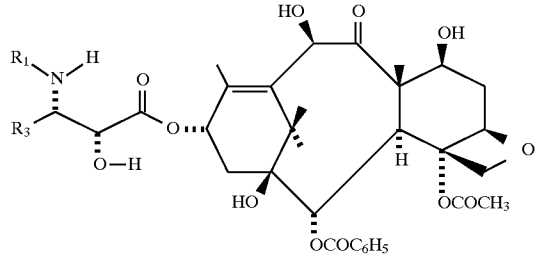


(XIX)

which, by the action of a product of general formula (XV), yields the product of general formula (V), the protective groups of which are replaced by hydrogen atoms to give a product of general formula (I) in which Z represents a radical of general formula (II).

The reactions used for silylation, functionalization and replacement of the protective groups by hydrogen atoms are performed under conditions similar to those described above.

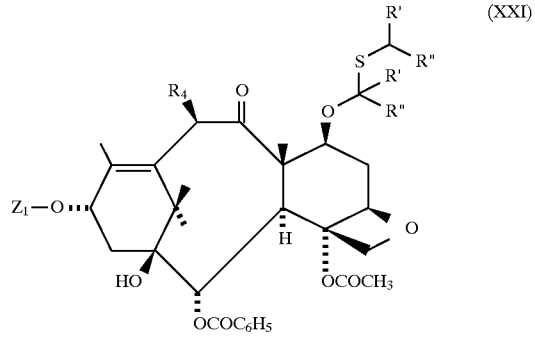
The products of general formula (XVI) may be obtained under the conditions described in European Patent EP 0,336,841 and international Applications PCT WO 92/09589 and WO 94/07878, the disclosures of which are hereby incorporated by reference in their entirety, or from the products of general formula (XX):



(XX)

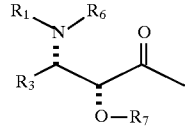
in which R_1 and R_3 are defined as above, according to known methods for protecting the hydroxyl function of the side chain without affecting the remainder of the molecule.

According to the invention, the products of general formula (I) in which Z represents a hydrogen atom or a radical of general formula (II) may be obtained by the action of activated Raney nickel, in the presence of an aliphatic alcohol containing 1 to 3 carbon atoms or an ether such as tetrahydrofuran or dioxane, on a product of general formula (XXI):



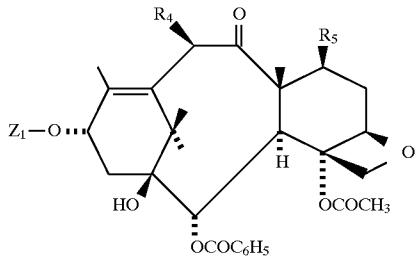
(XXI)

in which R_4 is defined as above and R' and R", which may be identical or different, represent a hydrogen atom or an alkyl radical containing 1 to 6 carbon atoms, an alkenyl radical containing 2 to 6 carbon atoms, an alkynyl radical containing 2 to 6 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms or a cycloalkenyl radical containing 3 to 6 carbon atoms, optionally substituted, or alternatively R' and R", together with the carbon atom to which they are linked, form a cycloalkyl radical containing 3 to 6 carbon atoms or a cycloalkenyl radical containing 4 to 6 carbon atoms, and Z_1 represents a hydrogen atom or a radical of general formula (XXII):



(XXII)

in which R_1, R_3, R_6 and R_7 are defined as above, and, to obtain a product of general formula (XXIII):

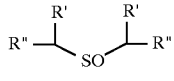


(XXIII)

followed, when Z_1 represents a radical of general formula (XXII), that is to say when the product of general formula (XXIII) is identical to the product of general formula (V), by replacement of the protective groups represented by R_6 and/or R_6 and R_7 by hydrogen atoms under the conditions described above.

Generally, the action of activated Raney nickel in the presence of an aliphatic alcohol or an ether is performed at a temperature of from −10° to 60° C.

According to the invention, the product of general formula (XXI) in which Z_1 and R_4 are defined as above may be obtained by the action of a sulphoxide of general formula (XXIV):



(XXIV)

in which R' and R" are defined as above, on a product of general formula (XIX).

Generally, the reaction of the sulphoxide of general formula (XXIV), preferably dimethyl sulphoxide, with the product of general formula (XIX) is performed in the presence of a mixture of acetic acid and acetic anhydride or a derivative of acetic acid such as a haloacetic acid at a temperature of from 0° to 50° C., and preferably at about 25° C.

The new products of general formula (I) obtained by carrying out the processes according to the invention may be purified according to known methods such as crystallization or chromatography.

The products of general formula (I) in which Z represents a radical of general formula (II) display noteworthy biological properties.

In vitro, measurement of the biological activity is performed on tubulin extracted from pig's brain by the method of M. L. Shelanski et al., Proc. Natl. Acad. Sci. USA, 70, 765–768 (1973). Study of the depolymerization of microtubules to tubulin is performed according to the method of G. Chauvière et al., C.R. Acad. Sci., 293, series II, 501–503 (1981). In this study, the products of general formula (I) in which Z represents a radical of general formula (II) were shown to be at least as active as taxol and Taxotere.

In vivo, the products of general formula (I) in which Z represents a radical of general formula (II) were shown to be active in mice grafted with B16 melanoma at doses of from 1 to 30 mg/kg administered intraperitoneally, as well as on other liquid or solid tumours.

The new products have antitumour properties, and more especially activity against tumours which are resistant to Taxol® or to Taxotere®. Such tumours comprise colon tumours which have a high expression of the mdr 1 gene (multiple drug resistance gene). Multiple drug resistance is a customary term relating to the resistance of a tumour to different products having different structures and mechanisms of action. Taxoids are generally known to be strongly recognized by experimental tumours such as P388/DOX, a cell line selected for its resistance to doxorubicin (DOX) which expresses mdr 1.

The examples which follow illustrate the present invention.

EXAMPLE 1

126 mg of dicyclohexylcarbodiimide and then 14 mg of 4-(N,N-dimethylamino)pyridine were added successively at a temperature in the region of 20° C. to a suspension containing 217.8 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,13α-dihydroxy-7β,10β-dimethoxy-9-oxo-11-taxene, 200 mg of (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylic acid and 50 mg of powdered 4 Å molecular sieve in 2 cm^3 of ethyl acetate. The suspension obtained was stirred at a temperature in the region of 20° C. under an argon atmosphere for 16 hours, and then concentrated to dryness under reduced pressure (0.27 kPa) at a temperature in the region of 40° C. The residue obtained was purified by chromatography at atmospheric pressure on 50 g of silica (0.063–0.2 mm) contained in a column 2 cm in diameter (elution gradient: ethyl acetateldichloromethane from 10:90 to 40:60 by volume), collecting 10-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 271.8 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy- 1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were thereby obtained in the form of a white solid, the characteristics of which were as follows:

^{1}H NMR spectrum (400 MHz; $CDCl_3$ with a few drops of CD_3OD-d_4; chemical shifts δ in ppm; coupling constants J in Hz): 1.02 (s, 9H: $C(CH_3)_3$); 1.10 (s, 3H: CH_3); 1.17 (s, 3H: CH_3); 1.63 (s, 3H: CH_3); from 1.65 to 1.85 and 2.60 (2 mts, 1H each; CH_2 at position 6); 1.78 (unres. comp., 3H: CH_3); 2.02 and 2.15 (2 dd, J=14 and 9, 1H each: CH_2 at position 14); 2.14 (s, 3H: CH_3); 3.22 and 3.35 (2 s, 3H each: OCH_3); 3.64 (d, J=7, 1H: H at position 3); 3.73 (mt, 1H: H at position 7); 3.76 (s, 3H: $ArOCH_3$); 4.06 and 4.16 (2 d, J=8.5, 1H each; CH_2 at position 20); 4.53 (d, J=5, 1H: H at position 2'); 4.67 (s, 1H: H at position 10); 4.85 (broad d, J=10, 1H: H at position 5); 5.36 (mt, 1H: H at position 3'); 5.52 (d, J=7, 1H: H at position 2); 6.07 (mt, 1H: H at position 13); 6.33 (unres. comp., 1H: H at position 5'); 6.88 (d, J=8, 2H: aromatic H at the ortho position with respect to OCH_3); from 7.25 to 7.40 (mt, 7H: aromatic H at position 3' and aromatic H at the meta position with respect to OCH_3); 7.43 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.58 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 7.96 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

A solution of 446.3 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in 11.6 cm^3 of a 0.1N solution of hydrogen chloride in ethanol was stirred constantly at a temperature in the region of 0° C. for 16 hours under an argon atmosphere. The reaction mixture was then diluted with 40 cm^3 of dichloromethane and 5 cm^3 of distilled water. After settling had taken place, the aqueous phase was separated and extracted with 5 cm^3 of dichloromethane. The organic phases were combined, dried over magnesium sulphate, filtered through sintered glass and then concentrated to dryness under reduced pressure (0.27 kPa) at a temperature in the region of 40° C. 424.2 mg of a pale yellow solid were obtained, which product was purified by preparative thin-layer chromatog-

raphy [12 Merck preparative silica gel $60F_{254}$ plates, thickness 1 mm, application in solution in a methanol/dichloromethane (5:95 by volume) mixture, eluting with a methanol/dichloromethane (5:95 by volume) mixture]. After elution of the zone corresponding to the main product with a methanol/dichloromethane (15:85 by volume) mixture, filtration through sintered glass and evaporation of the solvents under reduced pressure (0.27 kPa) at a temperature in the region of 40° C., 126 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate were obtained in the form of an ivory-coloured foam, the characteristics of which were as follows:

optical rotation $[\alpha]_{20}^{D}$=−32.9 (c=0.5; methanol)

^{1}H NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling constants J in Hz): 1.23 (s, 3H: CH_3); 1.25 (s, 3H: CH_3); 1.39 (s, 9H: $C(CH_3)_3$); 1.70 (s, 1H: OH at position 1); 1.75 (s, 3H: CH_3); 1.82 and 2.72 (2 mts, 1H each: CH_2 at position 6); 1.91 (s, 3H: CH_3); 2.31 (limiting AB, 2H: CH_2 at position 14); 2.39 (s, 3H: $COCH_3$); 3.33 and 3.48 (2 s, 3H each: OCH_3); 3.48 (mt, 1H: OH at position 2'); 3.85 (d, J=7, 1H: H 3); 3.88 (dd, J=11 and 7, 1H: H 7); 4.20 and 4.33 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.65 (mt, 1H: H at position 2'); 4.83 (s, 1H: H at position 10); 5.00 (broad d, J=10, 1H: H at position 5); 5.30 (broad d, J=10, 11H: H at position 3'); 5.47 (d, J=10, 1H: CONH); 5.66 (d, J=7, 1H: H at position 2); 6.24 (broad t, J=9, 1H: H at position 13); from 7.30 to 7.50 (mt, 5H: aromatic H at position 3'); 7.52 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.63 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.12 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,13α-dihydroxy-7β,10β-dimethoxy-9-oxo-11-taxene (or 7β,10β-dimethoxy-10-deacetoxybaccatin III) was prepared in the following manner:

86 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin were added portionwise to a solution, maintained under an argon atmosphere, at a temperature in the region of 0° C., of 500 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-methoxy-9-oxo- 11-taxene in 5 cm^3 of iodomethane and 0.5 cm^3 of dimethylformamide. After 45 minutes at a temperature in the region of 0° C., the reaction mixture was diluted with 50 cm^3 of ethyl acetate and 8 cm^3 of distilled water. After settling had taken place, the organic phase was separated and washed with twice 8 cm^3 of distilled water and then 8 cm^3 of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (0.27 kPa) at a temperature in the region of 40° C. 570 mg of a pale yellow solid were thereby obtained, which product was purified by chromatography at atmospheric pressure on 50 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter, eluting with a methanol/dichloromethane (2:98 by volume) mixture and collecting 10-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 380 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,13α-dihydroxy-7β,10β-dimethoxy-9-oxo-11-taxene were thereby obtained in the form of a pale yellow solid, the characteristics of which were as follows:

^{1}H NMR spectrum (400 MHz; $CDCl_3$; with a few drops of CD_3OD-d_4, chemical shifts δ in ppm; coupling constants J in Hz): 1.03 (s, 3H: CH_3); 1.11 (s, 3H: CH_3); 1.65 (s, 3H: CH_3); 1.72 and 2.67 (2 mts, 1H each: CH_2 at position 6); 2.05 (s, 3H: CH_3): 2.21 (limiting AB, J=14 and 9, 2H: CH_2 at position 14); 2.25 (s, 3H: $COCH_3$); 3.26 and 3.40 (2 s, 3H each: OCH_3); 3.85 (d, J=7, 1H: H at position 3); 3.89 (dd, J=11 and 6.5, 1H: H at position 7); 4.12 and 4.25 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.78 (broad t, J=9, 1H: H at position 13); 4.83 (s, 1H: H at position 10); 4.98 (broad d, J=10, 1H: H at position 5); 5.53 (d, J=7, 1H: H at position 2); 7.43 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.56 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.05 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-methoxy-9-oxo-11-taxene (or 10β-methoxy-10-deacetoxybaccatin III) was prepared in the following manner:

50 cm^3 of hydrogen fluoride/triethylamine complex (3HF.Et_3N) were added slowly to a solution, maintained under an argon atmosphere, at a temperature in the region of 0° C., of 3.62 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-methoxy-9-oxo-7β,13α-bis(triethylsilyoxy)-11-taxene in 30 cm^3 of dichloromethane. After 48 hours at a temperature in the region of 20° C., the reaction mixture was poured into a suspension of 100 cm^3 of supersaturated aqueous sodium hydrogen carbonate solution maintained at a temperature in the region of 0° C. After settling had taken place, the aqueous phase was separated and re-extracted with three times 80 cm^3 of dichloromethane and then twice 80 cm^3 of ethyl acetate. The organic phases were combined, dried over magnesium sulphate, filtered through magnesium sulphate and concentrated to dryness under reduced pressure (0.27 kPa) at a temperature in the region of 40° C. 3.45 g of a yellow foam were thereby obtained, which product was purified by chromatography at atmospheric pressure on 150 g of silica (0.063–0.2 mm) contained in a column 3.5 cm in diameter, eluting with a methanol/dichloromethane (5:95 by volume) mixture and collecting 35-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 1.97 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-methoxy-9oxo-11-taxene were thereby obtained in the form of a white solid, the characteristics of which were as follows:

^{1}H NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm: coupling constants J in Hz): 1.10 (s, 3H: CH_3); 1.19 (s, 3H: CH_3); 1.48 (d, J=8.5, 1H: OH at position 13); 1.70 (s, 3H: CH_3); 1.81 and 2.61 (2 mts, 1H each: CH_2 at position 6); 2.09 (d, J=5, 1H: OH at position 7); 2.11 (s, 3H: CH_3); 2.30 (s, 3H: $COCH_3$); 2.32 (d, J=9, 2H: CH_2 at position 14); 3.48 (s, 3H: OCH_3); 3.97 (d, J=7, 1H: H at position 3); 4.18 and 4.33 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.31 (mt, 1H: H at position 7); 4.93 (mt, 1H: H at position 13); 4.99 (s, 1H: H at position 10); 5.01 (broad d, J=10, 1H: H at position 5); 5.66 (d, J=7, 1H: H at position 2); 7.49 (t, J=7.5, 2H: $OCOC_8H_5$ H at the meta position); 7.63 (t, J=7.5, 1H: $OCOC_8H_5$ H at the para position); 8.12 (d, J=7.5, 2H: $OCOC_8H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-methoxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene (or 10β-methoxy-10-deacetoxy-7,13-bis(triethylsilyl) baccatin III) was prepared in the following manner:

375 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin were added portionwise to a solution, maintained under an argon atmosphere, at a temperature in the region of 0° C., of 5 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-

bis(triethylsilyloxy)-11-taxene in 25 cm^3 of iodomethane. The solution was stirred constantly for 45 minutes at a temperature in the region of 0° C., and then for 5 hours 30 minutes at a temperature in the region of 20° C. The reaction mixture was cooled again to a temperature in the region of 0° C., and 125 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin were added portionwise. After 1 hour at 20° C. and then 18 hours at 5° C., the reaction mixture was diluted by adding 50 cm^3 of dichloromethane and poured into 50 cm^3 of saturated aqueous ammonium chloride solution, and settling was allowed to take place. The aqueous phase was separated and extracted with twice 30 cm^3 of dichloroemethane, and the organic phases were then combined, washed with 10 cm^3 of distilled water, dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (0.27 kPa) at a temperature in the region of 40° C. 5.15 g of a yellow foam were thereby obtained, which product was purified by chromatography at atmospheric pressure on 300 g of silica (0.063–0.2 mm) contained in a column 5 cm in diameter (elution gradient: ethyl acetate/dichloromethane from 0:100 to 10:90 by volume), collecting 30-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 3.62 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-methoxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene were thereby obtained in the form of a pale yellow foam, the characteristics of which were as follows:

^{1}H NMR spectrum (600 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling constants J in Hz): 0.58 and 0.69 (2 mts, 6H each: ethyl CH_2); 0.97 and 1.04 (2 t, J=7.5, 9H each: ethyl CH_3); 1.15 (s, 3H: CH_3); 1.18 (s, 3H: CH_3); 1.58 (s, 1H: OH at position 1); 1.68 (s, 3H: CH_3); 1.89 and 2.48 (2 mts, 1H each: CH_2 at position 6); 2.04 (s, 3H: CH_3); 2.15 and 2.23 (2 dd, J=16 and 9, 1H each: CH_2 at position 14); 2.29 (s, 3H: $COCH_3$); 3.40 (s, 3H: OCH_3); 3.83 (d, J=7, 1H: H: H at position 13); 4.15 and 4.30 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.43 (dd, J=11 and 7, 1H: H at position 7); 4.91 (s 1H: H at position 10); 4.96 (broad d, J=10, 1H at position 5); 5.01 (broad t, J=9, 1H: H at position 13); 5.62 (d, J=7, 1H: H at position 2); 7.46 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.60 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.09 (d, J=7.5, 2H: $OCOC_8H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene (or 10-deacetyl-7,13-bis(triethylsilyl)baccatin III) was prepared in the following manner:

10.8 cm^3 of triethylsilyl chloride were added to a solution, maintained under an argon atmosphere, at a temperature in the region of 20° C., of 14 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,10β,13α-tetrahydroxy-9-oxo-11-taxene (10-deacetylbaccatin III) in 50 cm^3 of anhydrous pyridine. After 17 hours at a temperature in the region of 20° C., the reaction mixture was brought to a temperature in the region of 115° C. and 10.8 cm^3 of triethylsilyl chloride were then added. After 3 hours 15 minutes at a temperature in the region of 115° C., the reaction mixture was brought back to a temperature in the region of 20° C. and diluted with 30 cm^3 of ethyl acetate and 100 cm^3 of distilled water. After settling took place, the aqueous phase was separated and extracted with twice 50 cm^3 of ethyl acetate. The organic phases were combined, washed with 50 cm^3 of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through sintered glass and then concentrated to dryness under reduced pressure (0.27 kPa) at a temperature in the region of 40° C. 63.1 g of a brown oil were thereby obtained, which product was purified by chromatography at atmospheric pressure on 800 g of silica (0.063–0.2 mm) contained in a column 7 cm in diameter (elution gradient: ethyl acetate/dichloromethane from 0:100 to 5:95 by volume), collecting 60-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 9.77 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene were thereby obtained in the form of a cream-coloured foam, the characteristics of which were as follows:

^{1}H NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling constants J in Hz): 0.55 and 0.68 (2 mts, 6H each: ethyl CH_2); 0.94 and 1.03 (2 t, J=7.5, 9H each: ethyl CH_3); 1.08 (s, 3H: CH_3); 1.17 (s, 3H: CH_3); 1.58 (s, 1H: OH at position 1); 1.73 (s, 3H: CH_3); 1.91 and 2.57 (2 mts, 1H each: CH_2 at position 2); 2.04 (s, 3H: CH_3); 2.12 and 2.23 (2 dd, J=16 and 9, 1H each: CH_2 at position 14); 2.30 (s, 3H: $COCH_3$); 3.88 (d, J=7, 1H: H at position 3); 4.16 and 4.32 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.27 (d, J=1, 1H: OH at position 10); 4.40 (dd, J=11 and 7, 1H: H at position 7); 4.95 (broad d, J=10, 1H: H at position 5); 4.95 (mt, 1H: H at position 13): 5.16 (d, J=1, 1H: H at position 10); 5.60 (d, J=7, 1H: H at position 2); 7.46 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.60 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.09 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

EXAMPLE 2

340 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were dissolved in 8 cm^3 of a 0.1N ethanolic solution of hydrochloric acid containing 1% of water. The solution thereby obtained was stirred for 13 hours at a temperature in the region of 20° C. and then for 80 hours at 4° C., and 20 cm^3 of dichloromethane were added. The organic phase was separated after settling had taken place and washed successively with 3 times 5 cm^3 of saturated aqueous sodium hydrogen carbonate solution, dried over magnesium sulphate, filtered and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. 300 mg of a white foam were obtained, which product was purified by chromatography on silica gel deposited on plates [gel 1 mm thick, plates is 20×20 cm, eluent: dichloromethane/methanol (95:5 by volume)] in 80-mg fractions (4 plates). After localization with UV rays of the zone corresponding to the adsorbed desired product, this zone was scraped off, and the silica collected was washed on sintered glass with 10 times 5 cm^3 of ethyl acetate. The filtrates were combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. A white foam was obtained, which was repurified according to the same technique [3 plates; 20×20×1 mm; eluent: dichloromethane/ethyl acetate (90:10 by volume)]. 205 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate were thereby obtained in the form of a white foam, the characteristics of which were as follows:

optical rotation: $[\alpha]_{20}^{D}$=−33 (c=0.5; methanol).

^{1}H NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling constants J in Hz): 1.23 (s, 3H: —CH_3); 1.25 (s, 3H: —CH_3); 1.39 [s, 9H: —$C(CH_3)_3$]; 1.70 (s, 1H: —OH at position 1); 1.75 (s, 3H: —CH_3); 1.82 and 2.72 (2 mts, 1H each: —CH_2 at position 6); 1.91 (s, 3H: —CH_3);

2.31 (limiting AB, 2H: —CH_2 at position 14); 2.39 (s, 3H: —$COCH_3$); 3.33 and 3.48 (2 s, 3H each: —OCH_3); 3.48 (mt, 1H: OH at position 2'); 3.85 (d, J=7, 1H: —H at position 3); 3.88 (dd, J=11 and 7, 1H: —H at position 7); 4.20 and 4.33 (2d, J=8.5, 1H each: —CH_2 at position 20); 4.65 (mt, 1H: —H at position 2'); 4.83 (s, 1H: —H at position 10); 5.00 (broad d, J=10, 1H: —H at position 5); 5.30 (broad d, J=10, 1H: —H at position 3'); 5.47 (d, J=10, 1H: —CONH—); 5.66 (d, J=7, 1H: —H at position 2); 6.24 (broad t, J=9, 1H: —H at position 13); from 7.30 to 7.50 (mt, 5H: —C_6H_5 at position 3'); 7.52 [t, J=7.5, 2H: —$OCOC_8H_5$ (—H at position 3 and H at position 5)]; 7.63 [t, J=7.5, 1H: —$OCOC_6H_5$ (—H at position 4)]; 8.12 [d, J=7.5, 2H: —$OCOC_8H_5$ (—H at position 2 and H at position 6)].

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate was prepared in the following manner:

100 cm^3 of an ethanolic suspension of activated nickel according to Raney (obtained from 80 cm^3 of the approximately 50% commercial aqueous suspension by successive washing, to a pH in the region of 7, with 15 times 100 cm^3 of distilled water and with 5 times 100 cm^3 of ethanol) were added at a temperature in the region of 20° C. to a solution, maintained under an argon atmosphere and kept stirring, of 1 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-bis(methylthiomethoxy)-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in 100 cm^3 of anhydrous ethanol. The reaction medium was kept stirring for 24 hours at a temperature in the region of 20° C. and then filtered through sintered glass. The sintered glass was washed with 4 times 80 cm^3 of ethanol, and the filtrates were combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. 710 mg of a yellow foam were obtained, which product was purified by chromatography on 60 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter [eluent: dichloromethane/ethyl acetate (90:10 by volume)], collecting 6-cm^3 fractions. Fractions containing only the desired product are pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. 350 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were thereby obtained in the form of a white foam.

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-bis(methylthiomethoxy)-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxy-phenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate was prepared in the following manner:

2.3 cm^3 of acetic acid and 7.55 cm^3 of acetic anhydride were added at a temperature in the region of 20° C. to a solution, maintained under an argon atmosphere and kept stirring, of 3.1 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,10β-trihydroxy-9oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate dissolved in 102 cm^3 of dimethyl sulphoxide. The reaction mixture was kept stirring for 7 days at a temperature in the region of 20° C., and then poured into a mixture of 500 cm^3 of distilled water and 250 cm^3 of dichloromethane. 30 cm^3 of saturated aqueous potassium carbonate solution were then added with efficient stirring to a pH in the region of 7. After 10 minutes of stirring, the organic phase was separated after settling had taken place and the aqueous phase was re-extracted with twice 250 cm^3 of dichloromethane. The organic phases were combined, washed with 250 cm^3 of distilled water, dried over magnesium sulphate, filtered and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. 5.2 g of a pale yellow oil were obtained, which product was purified by chromatography on 200 g of silica (0.063–0.4 mm) contained in a column 3 cm in diameter [eluent: dichloromethane/methanol (99:1 by volume)], collecting 50-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. 1.25 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-bis(methylthiomethoxy)-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were thereby obtained in the form of a white foam.

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,10β-trihydroxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate was prepared in the following manner:

A solution of 5.1 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-9-oxo-7β,10β-bis(2,2,2-trichloroethoxycarbonyloxy)-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in a mixture of 100 cm^3 of methanol and 100 cm^3 of acetic acid was heated, with stirring and under an argon atmosphere, to a temperature in the region of 60° C., and 10 g of powdered zinc were then added. The reaction mixture was then stirred for 15 minutes at 60° C., thereafter cooled to a temperature in the region of 20° C. and filtered through sintered glass lined with Celite. The sintered glass was washed with twice 15 cm^3 of methanol. The filtrate was concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40° C. 50 cm^3 of ethyl acetate and 25 cm^3 of saturated aqueous sodium hydrogen carbonate solution were added to the residue. The organic phase was separated after settling had taken place and washed successively with 25 cm^3 of saturated aqueous sodium hydrogen carbonate solution and with 25 cm^3 of distilled water, then dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. 3.1 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,10β-trihydroxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were thereby obtained in the form of a white foam.

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-9-oxo-7β,10β-bis(2,2,2-trichloroethoxy-carbonyloxy)-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxy-carbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate was prepared under the conditions described in Patent WO 94/07878, the disclosure of which is specifically incorporated by reference herein.

EXAMPLE 3

76 mg of dicyclohexylcarbodiimide and then 8.5 mg of 4-N,N-dimethylamino)pyridine were added successively at a temperature in the region of 20° C. to a suspension containing 135 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene, 120 mg of (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylic acid and 50 mg of powdered 4 Å molecular sieve in 1 cm^3 of anhydrous toluene. The suspension obtained was stirred at

a temperature in the region of 20° C. under an argon atmosphere for 1 hour, and then purified by direct application to a column for chromatography at atmospheric pressure on 30 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter (elution gradient: ethyl acetate/dichloromethane from 2:98 to 10:90 by volume), collecting 10-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. for 2 hours. 320.6 mg of a white solid were thereby obtained, which product was purified by preparative thin-layer chromatography: 10 Merck preparative silica gel 60F_{254} plates, thickness 0.5 mm, application in solution in dichloromethane, eluting with a methanol/dichloromethane (3:97 by volume) mixture. After elution of the zones corresponding to the main products with a methanol/dichloromethane (15:85 by volume) mixture, filtration through cotton wool and then evaporation of the solvents under reduced pressure (2.7 kPa) at a temperature in the region of 40° C., 47.7 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene were obtained in the form of a cream-coloured solid and 37 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were obtained in the form of a white foam, the characteristics of which 5-carboxylate product were as follows:

^{1}H NMR spectrum (600 MHz; $CDCl_3$; at a temperature of 333 K; chemical shifts δ in ppm; coupling constants J in Hz): 1.09 (s, 9H: $C(CH_3)_3$; 1.19 (s, 3H: CH_3); 1.21 (s, 3H: CH_3); 1.27 (t, J=7, 3H: ethyl CH_3); 1.43 (s, 1H: OH at position 1); 1.62 (s, 3H: CH_3); 1.68 (s, 3H: CH_3); 1.77 and 2.63 (2 mts, 1H each: CH_2 at position 6); 1.86 (s, 3H: $COCH_3$); 2.13 and 2.22 (2 dd, J=16 and 9, 1H each: CH_2 at position 14); 3.27 (s, 3H: OCH_3); 3.45 and 3.68 (2 mts, 1H each: ethyl CH_2); 3.76 (d, J=7, 1H: H3); 3.81 (s, 3H: $ArOCH_3$); 3.85 (dd, J=11 and 7, 1H: H at position 7); 4.13 and 4.23 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.58 (d, J=4.5, 1H: H at position 2'); 4.83 (s, 1H: H at position 10); 4.90 (broad d, J=10, 1H: H at position 5); 5.46 (d, J=4.5, 1H: H at position 3'); 5.60 (d, J=7 Hz, 1H: H2); 6.13 (broad t, J=9 Hz, 1H: H13); 6.38 (s, 1H: H5'); 6.92 (d, J=8.5, 2H: aromatic H at the ortho position with respect to OCH_3); from 7.30 to 7.50 (mt, 9H: aromatic H at position 3'-aromatic H at the meta position with respect to OCH_3 and $OCOC_6H_5$ H at the meta position); 7.59 (t, J=7.5, 1H: $OCOC_8H_5$ H at the para position); 8.03 (d, J=7.5, 2H: $OCOC_8H_5$ H at the ortho position).

A solution of 48 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in 0.5 cm^3 of ethyl acetate and 0.004 cm^3 of concentrated 37% hydrochloric acid was kept stirring at a temperature in the region of 20° C. for 1.5 hours under an argon atmosphere. The reaction mixture was then purified by preparative thin-layer chromatography: application of the crude reaction mixture to 5 Merck preparative silica gel 60F_{254} plates, thickness 0.5 mm, eluting with a methanol/dichloromethane (4:96 by volume) mixture. After elution of the zone corresponding to the main product with a methanol/dichloromethane (15:85 by volume) mixture, filtration through cotton wool and then evaporation of the solvents under reduced pressure (2.7 kPa) at a temperature in the region of 40° C., 28.5 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate were obtained in the form of an ivory-coloured foam, the characteristics of which were as follows:

^{1}H NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling constants J in Hz): 1.22 (s, 3H: CH_3); 1.25 (s, 3H: CH_3); 1.32 (t, J=7, 3H: ethyl CH_3); 1.38 (s, 9H: $C(CH_3)_3$; 1.64 (s, 1H: OH at position 1); 1.73 (s, 3H: CH_3); 1.80 and 2.70 (2 mts, 1H each: CH_2 at position 6); 1.88 (s, 3H: CH_3); 2.30 (mt, 2H; CH_2 at position 14); 2.38 (s, 3H: $COCH_3$); 3.31 (s, 3H: OCH_3); 3.44 (unres. comp., 1H: OH at position 2'); 3.50 and 3.70 (2 mts, 1H each ethyl OCH_2); 3.84 (d, J=7.5, 1H: H at position 3); 3.87 (dd, J=11 and 6.5, 1H: H at position 7); 4.18 and 4.32 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.64 (mt, 1H: H at position 2'); 4.90 (s, 1H: H at position 10); 4.98 (broad d, J=10, 1H: H at position 5); 5.28 (broad d, J=10, 1H: H at position 3'); 5.42 (d, J=10, 1H: CONH); 5.64 (d, J=7.5, 1H: H at position 2); 6.22 (broad t, J=9, 1H: H at position 13); from 7.25 to 7.45 (mt, 5H: aromatic H at position 3'); 7.50 (d, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.62 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.12 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene (or 10β-ethoxy-7β-methoxy-10-deacetoxybaccatin III) may be prepared in the following manner:

43 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin were added portionwise to a solution, maintained under an argon atmosphere, at a temperature in the region of 0° C., of 235 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-ethoxy-9-oxo-11-taxene in 2.5 cm^3 of iodomethane and 1 cm^3 of dimethylformamide After 30 minutes at a temperature in the region of 0° C., the reaction mixture was diluted with 40 cm^3 of ethyl acetate, 6 cm^3 of distilled water and 8 cm^3 of saturated aqueous ammonium chloride solution. After settling had taken place, the organic phase was separated and washed with three times 8 cm^3 of distilled water and then 8 cm^3 of saturated aqueous NaCl solution, dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40° C. 268 mg of a yellow solid were thereby obtained, which product was purified by chromatography at atmospheric pressure on 30 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter (elution gradient: ethyl acetate/dichloromethane from 0:100 to 15:85 by volume), collecting 10-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 380 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene are thereby obtained in the form of a white powder, the characteristics of which were as follows:

^{1}H NMR spectrum (300 MHz; $CDCl_3$ with the addition of a few drops of CD_3OD-d_4; chemical shifts δ in ppm, coupling constants J in Hz): 0.99 (s, 3H: CH_3); 1.09 (s, 3H: CH_3); 1.22 (t, J=7, 3H: ethyl CH_3); 1.62 (s, 3H: CH_3); 1.68 and 2.66 (2 mts, 1H each: CH_26); 2.03 (s, 3H, CH_3); 2.13 and 2.22 (2 dd, J=16 and 9, 1H each: CH_2 at position 14); 2.23 (s, 3H: $COCH_3$); 3.23 (s, 3H: OCH_3); from 3.40 to 3.65 (mt, 2H: ethyl CH_2); 3.84 (d, J=7.5, 1H: H at position 3); 3.88 (dd, J=10 and 6.5, 1H: H at position 7); 4.10 and 4.23 (2 d, J=8.5, 1H each: CH_2 20); 4.75 (broad t, J=9, 1H: H at position 13); 4.90 (s, 1H: H at position 10); 4.97 (broad d, J=10, 1H: H at position 5); 5.51 (d, J=7.5, 1H: H at position 2); 7.42 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position);

7.53 (t, J=7.5, 1H: $OCOC_6H_5$ at the para position); 8.03 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-ethoxy-9-oxo-11-taxene (or 10β-ethoxy-10-deacetoxybaccatin III) was prepared in the following manner:

9 cm^3 of hydrogen fluoride/triethylamine complex ($3HF.Et_3N$) were added to a solution, maintained under an argon atmosphere, at a temperature in the region of 20° C., of 591 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,hydroxy-10β-ethoxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene in 6 cm^3 of dichloromethane. After 21 hours at a temperature in the region of 20° C., the reaction mixture was diluted with 40 cm^3 of dichloromethane and poured into a suspension of 40 cm^3 of supersaturated aqueous sodium hydrogen carbonate solution maintained at a temperature in the region of 0° C. After dilution with 10 cm^3 of distilled water and when settling had taken place, the aqueous phase was separated and re-extracted with twice 20 cm^3 of diethyl ether. The organic phases were combined, washed with 20 cm^3 of distilled water and 20 cm^3 of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through magnesium sulphate and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40° C. 370 mg of a pale yellow foam were thereby obtained, which product is purified by chromatography at atmospheric pressure on 35 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter, eluting with a methanol/dichloromethane (2:98 by volume) mixture and collecting 15-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. for 2 hours. 236.2 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-ethoxy-9-oxo-11-taxene were thereby obtained in the form of a white solid, the characteristics of which were as follows:

^1H NMR spectrum (400 MHz; $CDCl_3$: chemical shifts δ in ppm, coupling constants J in Hz): 1.08 (s, 3H: CH_3); 1.19 (s, 3H: CH_3); 1.29 (t, J=7.5, 3H: ethyl CH_3); 1.38 (d, J=9, 1H: OH at position 7); 1.59 (s, 1H: OH at position 1); 1.69 (s, 3H: CH_3); 1.82 and 2.62 (2 mts, 1H each: CH_2 at position 6); 2.02 (d, J=5, 1H: OH at position 13); 2.08 (s, 3H: CH_3); 2.30 (s, 3H: $COCH_3$),; 2.32 (d, J=9, 2H: CH_2 at position 14); 3.56 and 3.67 (2 mts, 1H each: ethyl OCH_2); 3.98 (d, J=7, 1H: H at position 3); 4.18 and 4.33 (2 d, J=8.5 Hz, 1H each: CH_220); 4.30 (mt, 1H: H7); 4.90 (mt, 1H: H at position 13); 4.99 (dd, J=10 and 1.5, 1H: H at position 5); 5.05 (s, 1H: H at position 10); 5.66 (d, J=7, 1H: H at position 2); 7.49 (t, J=7.5, 2H: $OCOC_8H_5$ H at the meta position); 7.63 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.12 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-ethoxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene (or 10β-ethoxy-10-deacetoxy-7,13-bis(triethylsilyl)baccatin III) was prepared in the following manner:

93 mg of sodium hydride at a concentration of 50% by weight of liquid paraffin were added portionwise to a solution, maintained under an argon atmosphere, at a temperature in the region of 20° C., of 1 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene in 3 cm^3 of iodoethane and 4 cm^3 of dimethylformamide. The solution was kept stirring for 17 hours at a temperature in the region of 20° C., and 93 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin was then added portionwise. After 50 minutes at a temperature in the region of 20° C., the reaction mixture was diluted with 100 cm^3 of ethyl acetate and 10 cm^3 of saturated aqueous ammonium chloride solution. The organic phase was separated after settling had taken place and washed with six times 10 cm^3 of distilled water and then 10 cm^3 of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40° C. 1.2 g of a yellow foam were thereby obtained, which product was purified by chromatography at atmospheric pressure on 150 g of silica (0.063–0.2 mm) contained in a column 3.5 cm in diameter, eluting with an ethyl acetateldichloromethane (2:98, then 5:95 by volume) mixture and collecting 15-cm^3 fractions. Fractions containing only the desired products were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 379.2 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene were thereby obtained in the form of a pale yellow foam and 430 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-ethoxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene were thereby obtained in the form of a white foam, the characteristics of which 10-β-ethoxy product were as follows:

^1H NMR spectrum (400 MHz, $CDCl_3$; chemical shifts δ in ppm, coupling constants J in Hz): 0.57 and 0.70 (2 mts, 6H each; ethyl CH_2); 0.97 and 1.03 (2 t, J=7.5, 9H each: ethyl CH_3); 1.13 (s, 3H: CH_3); 1.20 (s, 3H: CH_3); 1.29 (t, J=7.5, 3H: CH_3 of ethoxy at position 10); 1.58 (s, 1H: OH at position 1); 1.66 (s, 3H: CH_3); 1.89 and 2.58 (2 mts, 1H each: CH_2 at position 2); 2.03 (s, 3H: CH_3); 2.13 and 2.23 (2 dd, J=16 and 9, 1H each CH_2 at position 14); 2.30 (s, 3H: $COCH_3$); 3.53 (mt, 2H: CH_2 of ethoxy at position 10); 3.84 (d, J=7, 1H: H at position 3); 4.15 and 4.30 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.43 (dd, J=11 and 6.5, 1H: H at position 7); from 4.90 to 5.00 (mt, 2H: H at position 13 and H at position 5), 5.01 (s, 1H: H at position 10); 5.61 (d, J=7, 1H: H at position 2); 7.48 (t, J=7.5, 2H: $OCOC_8H_5$ H at the meta position); 7.61 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.10 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

EXAMPLE 4

65 mg of dicyclohexylcarbodiimide and then 7 mg of 4-(N,N-dimethylaminopyridine were added successively at a temperature in the region of 20° C. to a suspension containing 115 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-(1-propyl)oxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene and 100 mg of (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylic acid in 1 cm^3 of anhydrous toluene. The suspension obtained was stirred at a temperature in the region of 20° C. under an argon atmosphere for 1 hour, and then purified by direct application to a column for chromatography at atmospheric pressure on 30 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter (elution gradient: ethyl acetate/dichloromethane from 2:98 to 10:90 by volume), collecting 10-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. for 2 hours. 276.2 mg of a white solid were thereby obtained, which product was purified by preparative thin-layer chromatography: 10 Merck preparative silica gel $60F_{254}$ plates, thickness 0.5 mm, application in solution in dichloromethane, eluting with a methanol/dichloromethane (3:97 by volume) mixture. After elution of the zones corresponding to the main products with a methanolldichloromethane (15:85 by volume) mixture, filtration through

cotton wool and then evaporation of the solvents under reduced pressure (2.7 kPa) at a temperature in the region of 40° C., 84.8 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-(1-propyl)oxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were obtained in the form of a white foam, the characteristics of which were as follows:

^{1}H NMR spectrum (300 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling constants J in Hz): 0.97 (t, J=7, 3H: propyl CH_3); 1.07 (s, 9H: $C(CH_3)_3$); 1.19 (s, 6H: CH_3); from 1.50 to 1.80 (mt, 3H: OH at position 1 and central CH_2 of propyl); 1.60 (s, 3H: CH_3); 1.70 (s, 3H: CH_3); 1.78 and 2.63 (2 mts, 1H each: CH_2 at position 6); 1.82 (unres. comp. 3H: $COCH_3$); 2.07 and 2.19 (2 dd, J=16 and 9, 1H each: CH_2 at position 14); 3.26 (s, 3H: OCH_3); 3.30 and 3.58 (2 mts, 1H each: propyl OCH_2); 3.73 (d, J=7.5, 1H: H at position 3); 3.81 (s, 3H: $ArOCH_3$); 3.81 (mt, 1H: H at position 7); 4.09 and 4.23 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.57 (d, J=4.5, 1H: H at position 2'); 4.79 (s, 1H: H at position 10); 4.90 (broad d, J=10, 1H: H at position 5); 5.40 (unres. comp. 1H: H at position 3'); 5.58 (d, J=7.5, 1H: H at position 2); 6.13 (broad t, J=9, 1H: H at position 13); 6.40 (spread unres. comp 1H: H at position 5'); 6.92 (d, J=8.5, 2H: aromatic H at the ortho position with respect to OCH_3); from 7.30 to 7.60 (mt, 9H: aromatic H at position 3'-aromatic H at the meta position with respect to OCH_3 and $OCOC_6H_5$ meta H); 7.63 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.03 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-(1-propyl)oxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate was prepared in the following manner:

A solution of 84 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-(1-propyl)oxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxy-carbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in 0.84 cm^3 of ethyl acetate and 0.0071 cm^3 of concentrated 37% hydrochloric acid was kept stirring at a temperature in the region of 20° C. for 1 hour under an argon atmosphere. The reaction mixture was then purified by preparative thin-layer chromatography: application of the crude reaction mixture to 6 Merck preparative silica gel $60F_{254}$ plates, thickness 0.5 mm, eluting with a methanol/acetonitrile/dichloromethane (3:7:90 by volume) mixture. After elution of the zone corresponding to the main product with a methanol/dichloromethane (15:85 by volume) mixture, filtration through cotton wool and then evaporation of the solvents under reduced pressure (2.7 kPa) at a temperature in the region of 40° C., 27 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-(1-propyl)oxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl(2R ,3S)-3tert-butoxycarbonylamino-2-hydroxy-3-phenyl-propionate were obtained in the form of a white foam, the characteristics of which are as follows:

^{1}H NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling constants J in Hz): 0.99 (t, J=7, 3H: propyl CH_3); 1.22 (s, 3H: CH_3); 1.25 (s, 3H: CH_3); 1.38 (s, 9H: $C(CH_3)_3$; 1.64 (s, 1H: OH at position 1); 1.69 (mt, 2H: central CH_2 of propyl); 1.73 (s, 3H: CH_3); 1.80 and 2.70 (2 mts, 1H each: CH_2 at position 6); 1.88 (s, 3H: CH_3); 2.30 (mt, 2H: CH_2 at position 14): 2.38 (s, 3H: $COCH_3$); 3.31 (s, 3H: OCH_3); 3.36 and 3.64 (2 mts, 1H each: propyl OCH_2); 3.44 (unres. comp. 1H: OH at position 2'); 3.84 (d, J=7.5, Hz, 1H: H at position 3); 3.87 (dd, J=11 and 6.5, 1H: H at position 7); 4.18 and 4.30 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.64 (mt, 1H: H at position 2'); 4.89 (s, 1H: H at position 10); 4.98 (broad d, J=10, 1H: H at position 5); 5.28 (broad d, J=10, 1H: H at position 3'); 5.42 (d, J=10, 1H: CONH); 5.64 (d, J=7.5, 1H: H at position 2); 6.22 (broad t, J=9, 1H: H at position 13); from 7.25 to 7.45 (mt, 5H: aromatic H at position 3'); 7.50 (d, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.61 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.12 (d, J=7.5, 2H: $OCOC_8H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-(1-propyl)oxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene (or 10β-(1-propyl)oxy-7β-methoxy-10-deacetoxybaccatin III) was prepared in the following manner:

30 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin were added portionwise to a solution, maintained under an argon atmosphere, at a temperature in the region of 0° C., of 165 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-(1-propyl)oxy-9-oxo-11-taxene in 1.7 cm^3 of iodomethane and 1 cm^3 of dimethylformamide. After 30 minutes at a temperature in the region of 0° C., the reaction mixture was diluted with 40 cm^3 of ethyl acetate, 5 cm^3 of distilled water and 7 cm^3 of saturated aqueous ammonium chloride solution. After settling had taken place, the organic phase was separated and washed with three times 7 cm^3 of distilled water and then 7 cm^3 of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40° C. 224 mg of the yellow solid were thereby obtained, which product was purified by chromatography at atmospheric pressure on 20 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter (elution gradient: ethyl acetate/dichloromethane from 0:100 to 15:85 by volume), collecting 10-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 117.5 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-(1-propyl)oxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene were thereby obtained in the form of a white foam, the characteristics of which were as follows:

^{1}H NMR spectrum (300 MHz; $CDCl_3$; chemical shifts δ in ppm, coupling constants J in Hz): 0.98 (t, J=7, 3H: propyl CH_3); 1.05 (s, 3H: CH_3), 1.19 (s, 3H: CH_3); from 1.60 to 1.80 (mt, 2H: central CH_2 of propyl); from 1.65 to 1.85 and 2.66 (2 mts, 1H each: CH_2 at position 6); 1.72 (s, 3H: CH_3); 2.10 (s, 3H: CH_3); from 2.05 to 2.35 (mt, 2H: CH_2 at position 14); 2.28 (s, 3H: $COCH_3$); 3.32 (s, 3H: OCH_3); 3.45 and 3.65 (2 mts, 1H each: propyl OCH_2); 3.92 (d, J=7.5, 1H: H3); 3.93 (dd, J=11 and 6, 1H: H at position 7); 4.16 and 4.32 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.90 (mt, 1H: H at position 13); 4.94 (s, 1H: H at position 10); 5.03 (broad d, J=10, 1H: H at position 5); 5.60 (d, J=7.5, 1H: H at position 2); 7.48 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.62 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.11 (d, J=7.5, 2H: $OCOC_8H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-(1-propyl)oxy-9-oxo-11-taxene (or 10β-(1-propyl)oxy-10-deacetoxybaccatin III) was prepared in the following manner:

8.75 cm^3 of hydrogen fluoride/triethylamine complex ($3HF.Et_3N$) were added to a solution, maintained under an argon atmosphere, at a temperature in the region of 20° C., of 585 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-(1-propyl)oxy-9-oxo-7β,13α-bis

(triethylsilyloxy)-11-taxene in 6 cm^3 of dichloromethane. After 24 hours at a temperature in the region of 20° C., the reaction mixture was diluted with 30 cm^3 of dichloromethane and poured into a suspension of 30 cm^3 of supersaturated aqueous sodium hydrogen carbonate solution maintained at a temperature in the region of 0° C. After dilution with 10 cm^3 of distilled water and when settling had taken place, the aqueous phase was separated and re-extracted with twice 20 cm^3 of diethyl ether. The organic phases were combined, washed with 20 cm^3 of distilled water and 20 cm^3 of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through magnesium sulphate and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40° C. 500 mg of a pale yellow foam were thereby obtained, which product was purified by chromatography at atmospheric pressure on 40 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter, eluting with a methanol/dichloromethane (2:98 by volume) mixture and collecting 15-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. for 2 hours. 373.8 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-(1-propyl)oxy-9-oxo-11-taxene were thereby obtained in the form of a white solid, the characteristics of which were as follows:

^{1}H NMR spectrum (300 MHz; $CDCl_3$; chemical shifts δ in ppm, coupling constants J in Hz): 0.95 (t, J=7, 3H: propyl CH_3); 1.06 (s, 3H: CH_3); 1.22 (s, 3H: CH_3); 1.45 (d, J=7.5, 1H: OH at position 7); from 1.60 to 1.80 (mt, 2H: central CH_2 of propyl); 1.67 (s, 3H: CH_3); 1.83 and 2.62 (2 mts, 1H each: CH_2 at position 6); 2.05 (s, 3H: CH_3); 2.05 (mt, 1H: OH at position 13); 2.27 (limiting AB, 2H: CH_2 at position 4); 2.28 (s, 3H: $COCH_3$); 3.40 and 3.57 (2 mts, 1H each: propyl OCH_2); 3.97 (d, J=7.5, 1H: H at position 3); 4.15 and 4.30 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.28 (mt, 1H: H at position 7); 4.90 (mt, 1H: H at position 13); 4.98 (broad d, J=10, 1H: H at position 5); 5.03 (s, 1H: H at position 10); 5.65 (d, J=7.5, 1H: H at position 2); 7.50 (t, J=7.5, 2H: $OCOC_8H_5$ H at the meta position); 7.60 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.00 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-(1-propyl)oxy-9-oxo-7β,13α-bis(triethyl-silyloxy)-11-taxene (or 10β-(1-propyl)oxy-10-deacetoxy-7,13-bis (triethylsilyl)baccatin III) was prepared in the following manner:

93 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin were added portionwise to a solution, maintained under an argon atmosphere, at a temperature in the region of 20° C., of 1 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene in 3 cm^3 of iodoethane and 4 cm^3 of dimethylformamide. The solution was kept stirring for 19 hours at a temperature in the region of 20° C., and 93 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin were then added portionwise. After 3 hours at a temperature in the region of 20° C., the reaction mixture was diluted with 100 cm^3 of ethyl acetate and 10 cm^3 of saturated aqueous ammonium chloride solution. The organic phase was separated after settling had taken place and washed with six times 10 cm^3 of distilled water and then 10 cm^3 of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40° C. 1.32 g of a pale yellow foam were thereby obtained, which product was purified by chromatography at atmospheric pressure on 150 g of silica (0.063–0.2 mm) contained in a column 3.5 cm in diameter, eluting with an ethyl acetate/dichloromethane (2:98, then 5:95 by volume) mixture and collecting 15-cm^3 fractions. Fractions containing only the desired products were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 376.3 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene were thereby obtained in the form of a pale yellow foam and 395.3 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-(1-propyl) oxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene were thereby obtained in the form of a pale yellow foam, the characteristics of which were as follows:

^{1}H NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm, coupling constants J in Hz); 0.57 and 0.70 (2 mts, 6H each: ethyl CH_2); 0.94 and 1.03 (2 t, J=7.5, 9H each: ethyl CH_3); 0.94 (t, J=7.5, 3H: propyl CH_3); 1.14 (s, 3H: CH_3); 1.21 (s, 3H: CH_3); 1.67 (s, 3H: CH_3); 1.69 (mt, 2H: central CH_2 of propyl); 1.88 and 2.48 (2 mts, 1H each: CH_2 at position 6); 2.03 (s, 3H: CH_3); 2.13 and 2.23 (2 dd, J=16 and 9, 1H each: CH_2 at position 14); 2.30 (s, 3H: $COCH_3$); 3.40 (mt, 2H: propyl OCH_2); 3.84 (d, J=7.5, 1H: H at position 3); 4.16 and 4.30 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.44 (dd, J=11 and 6.5, 1H: H at position 7); 4.96 (broad d, J=10 Hz, 1H: H5); 4.97 (s, 1H: H 10), 4.99 (broad t, J=9 Hz, 1H: H at position 13); 5.62 (d, J=7.5, 1H: H at position 2); 7.48 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.60 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.10 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

The new products of general formula (I) in which Z represents a radical of general formula (II) manifest significant inhibitory activity with respect to abnormal cell proliferation, and possess therapeutic properties permitting the treatment of patients having pathological conditions associated with abnormal cell proliferation. The pathological conditions include the abnormal cell proliferation of malignant or non-malignant cells of various tissues and/or organs, comprising, without implied limitation, muscle, bone or connective tissue, the skin, brain, lungs, sex organs, the lymphatic or renal systems, mammary or blood cells, liver, the digestive system, pancreas and thyroid or adrenal glands. These pathological conditions can also include psoriasis, solid tumours, cancers of the ovary, breast, brain, prostate, colon, stomach, kidney or testicles, Kaposi's sarcoma, cholangiocarcinoma, choriocarcinoma, neuroblastoma, Wilms' tumour, Hodgkin's disease, melanoma, multiple myeloma, chronic lymphocytic leukaemia and acute or chronic granulocytic lymphoma.

The new products according to the invention are especially useful for the treatment of cancer of the ovary. The products according to the invention may be used to prevent or delay the appearance or reappearance of the pathological conditions, or to treat these pathological conditions.

The products according to the invention may be administered to a patient according to different dosage forms suited to the chosen administration route, which is preferably the parenteral route. Parenteral administration comprises intravenous, intraperitoneal, intramuscular or subcutaneous administration. Intraperitoneal or intravenous administration is more especially preferred.

The present invention also comprises pharmaceutical compositions containing at least one product of general formula (I), in a sufficient amount suitable for use in human or veterinary therapy. The compositions may be prepared

according to the customary methods, using one or more pharmaceutically acceptable adjuvants, vehicles or excipients. Suitable vehicles include diluents, sterile aqueous media and various non-toxic solvents. Preferably, the compositions take the form of aqueous solutions or suspensions, injectable solutions which can contain emulsifying agents, colourings, preservatives or stabilizers. However, the compositions can also take the form of tablets, pills, powders or granules which can be administered orally.

The choice of adjuvants or excipients may be determined by the solubility and the chemical properties of the product, the particular mode of administration and good pharmaceutical practice.

For parenteral administration, sterile, aqueous or non-aqueous solutions or suspensions are used. For the preparation of non-aqueous solutions or suspensions, natural vegetable oils such as olive oil, sesame oil or liquid petroleum, or injectable organic esters such as ethyl oleate, may be used. The sterile aqueous solutions can consist of a solution of a pharmaceutically acceptable salt dissolved in water. The aqueous solutions are suitable for intravenous administration provided the pH is appropriately adjusted and the solution is made isotonic, for example with a sufficient amount of sodium chloride or glucose. The sterilization may be carried out by heating or by any other means which does not adversely affect the composition.

It is clearly understood that all the products participating in the compositions according to the invention must be pure and non-toxic in the amounts used.

The compositions can contain at least 0.01% of therapeutically active product. The amount of active product in a composition is such that a suitable dosage can be prescribed. Preferably, the compositions are prepared in such a way that a single dose contains from 0.01 to 1000 mg approximately of active product for parenteral administration.

The therapeutic treatment may be performed concurrently with other therapeutic treatments including antineoplastic drugs, monoclonal antibodies, immunotherapy or radiotherapy or biological response modifiers. The response modifiers include, without implied limitation, lymphokines and cytokines such as interleukins, interferons (α, β or δ) and TNF.

Other chemotherapeutic agents which are useful in the treatment of disorders due to abnormal cell proliferation include, without implied limitation, alkylating agents, for instance nitrogen mustards such as mechlorethamine, cyclophosphamide, melphalan and chlorambucil, alkyl sulphonates such as busulfan, nitrosoureas such as carmustine, lomustine, semustine and streptozocin, triazenes such as dacarbazine, antimetabolites such as folic acid analogues, for instance methotrexate, pyrimidine analogues such as fluorouracil and cytarabine, purine analogues such as mercaptopurine and thioguanine, natural products, for instance vinca alkaloids such as vinblastine, vincristine and vindesine, epipodophyllotoxins such as etoposide and teniposide, antibiotics such as dactinomycin, daunorubicin, doxorubicin, bleomycin, plicamycin and mitomycin, enzymes such as L-asparaginase, various agents such as coordination complexes of platinum, for instance cisplatin, substituted ureas such as hydroxyurea, methylhydrazine derivatives such as procarbazine, adrenocortical suppressants such as mitotane and aminoglutethimide, hormones and antagonists such as adrenocorticosteroids such as prednisone, progestins such as hydroxyprogesterone caproate, methoxyprogesterone acetate and megestrol acetate, oestrogens such as diethylstilboestrol and ethynyloestradiol, antioestrogens such as tamoxifen, and androgens such as testosterone propionate and fluoxymesterone.

The doses used for carrying out the methods according to the invention are those which permit a prophylactic treatment or a maximum therapeutic response. The doses vary according to the administration form, the particular product selected and features distinctive to the subject to be treated. In general, the doses are those which are therapeutically effective for the treatment of disorders due to abnormal cell proliferation.

The products according to the invention may be administered as often as necessary to obtain the desired therapeutic effect. Some patients may respond rapidly to relatively high or low doses, and then require low or zero maintenance doses. Generally, low doses will be used at the beginning of the treatment and, if necessary, increasingly stronger doses will be administered until an optimum effect is obtained.

For other patients, it may be necessary to administer maintenance doses 1 to 8 times a day, and preferably 1 to 4 times, according to the physiological requirements of the patient in question. It is also possible that some patients may require the use of only one to two daily administrations.

In man, the doses generally range from 0.01 to 200 mg/kg. For intraperitoneal administration, the doses will generally range from 0.1 to 100 mg/kg, preferably from 0.5 to 50 mg/kg and still more specifically from 1 to 10 mg/kg. For intravenous administration, the doses generally range from 0.1 to 50 mg/kg, preferably from 0.1 to 5 mg/kg and still more specifically from 1 to 2 mg/kg. It is understood that, in order to choose the most suitable dosage, account should be taken of the administration route, the patient's weight, general state of health and age and all factors which may influence the efficacy of the treatment.

The example which follows illustrates a composition according to the invention.

EXAMPLE

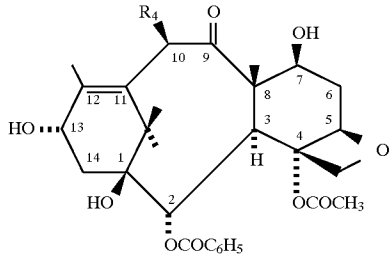
40 mg of the product obtained in Example 1 are dissolved in 1 cm^3 of Emulphor EL 620 and 1 cm^3 of ethanol, and the solution is then diluted by adding 18 cm^3 of physiological saline. The composition is administered by perfusion over 1 hour by introduction in physiological solution.

We claim:

1. 4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

2. A pharmaceutical composition comprising at least the product according to claim **1** in combination with one or more pharmaceutically acceptable diluents or adjuvants and optionally one or more compatible and pharmacologically active compounds.

3. A method comprising the step of etherifying selectively at position 7 a compound of the formula (XIV):



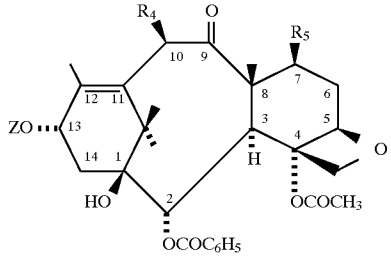
(XIV)

wherein R_4 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

with a compound of the formula (XV):

$$R'_5—X_2 \quad \text{(XV)}$$

wherein R'_5 represents a radical such that R'_5—O represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and X_2 represents a reactive ester residue or a halogen atom, to produce a compound of the formula (I):



(I)

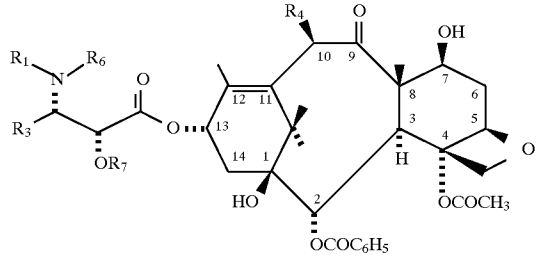
wherein Z is hydrogen, R_4 is as defined above, and R_5 is identical to R'_5 as defined above.

4. A method comprising the step of reacting a product of the formula (XV):

$$R'_5—X_2 \quad \text{(XV)}$$

wherein R'_5 represents a radical such that R'_5—O represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain, and X_2 represents a reactive ester residue or a halogen atom,

with a compound of the formula (XIX):



(XIX)

wherein R_1 represents a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, and trifluoromethyl radicals,

a thenoyl radical,

a furoyl radical, or

a radical R_2—O—CO— in which R_2 represents:

an alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents selected from halogen atoms; hydroxyl radicals; alkoxy radicals containing 1 to 4 carbon atoms; dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms; piperidino radicals; morpholino radicals; 1-piperazinyl radicals optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms; cycloalkyl radicals containing 3 to 6 carbon atoms; cycloalkenyl radicals containing 4 to 6 carbon atoms; phenyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms; cyano radicals; carboxyl radicals; and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms; alkyl radicals containing 1 to 4 carbon atoms; and alkoxy radicals containing 1 to 4 carbon atoms,

a 5-membered aromatic heterocyclic radical, or

a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

R_3 represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, or

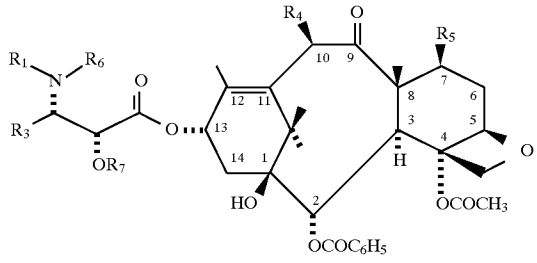
a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

with the proviso that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals in the definitions of R_2 and R_3, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

R_4 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain

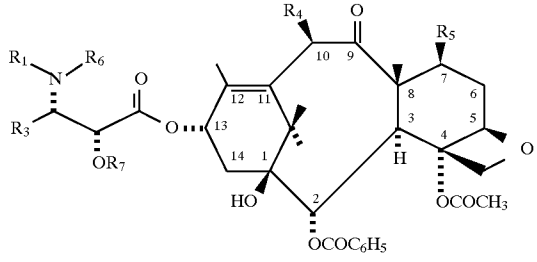
either R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, or R_6 and R_7 together form a saturated 5- or 6-membered heterocycle,

to form a compound of the formula (V):



wherein R_5 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and R_1, R_3, R_4, R_6, and R_7 are as defined above.

5. A method comprising the step of replacing with hydrogen atom(s) group(s) R_6 and R_7 in a compound of the formula (V):



wherein:

R_1 represents a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, and trifluoromethyl radicals,

a thenoyl radical,

a furoyl radical, or

a radical R_2—O—CO— in which R_2 represents:

an alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents selected from halogen atoms; hydroxyl radicals; alkoxy radicals containing 1 to 4 carbon atoms; dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms; piperidino radicals; morpholino radicals; 1-piperazinyl radicals optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms; cycloalkyl radicals containing 3 to 6 carbon atoms; cycloalkenyl radicals containing 4 to 6 carbon atoms; phenyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms; cyano radicals; carboxyl radicals; and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms; alkyl radicals containing 1 to 4 carbon atoms; and alkoxy radicals containing 1 to 4 carbon atoms,

a 5-membered aromatic heterocyclic radical, or

a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

R_3 represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, or

a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

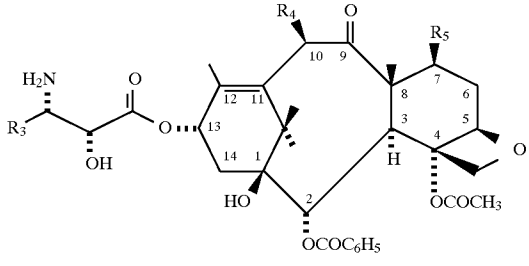
with the proviso that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals in the definitions of R_2 and R_3, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

R_4 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain

R_5 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and

either R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, or R_6 and R_7 together form a saturated 5- or 6-membered heterocycle,

by treating the compound of formula (V) with an organic or inorganic acid, optionally in an organic solvent to obtain a compound of the formula (VII):



(VII)

wherein R_3, R_4, and R_5 are as defined above.

6. A process for the preparation of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate, said process comprising:

converting 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-bis(methylthiomethoxy)-9-oxo-11-

taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate to said 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

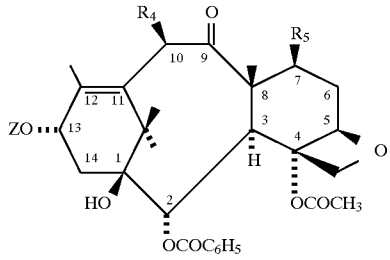
7. A process for the preparation of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate, said process comprising:

(a) reacting 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-7β,10β-trihydroxy-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate with dimethyl sulfoxide in the presence of acetic anhydride and acetic acid to obtain 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-bis(methylthiomethoxy)-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate;

(b) reacting the product obtained in (a) with activated Raney nickel to obtain 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tertbutoxy-carbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate; and

(c) reacting the product obtained in (b) with an acid to obtain 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

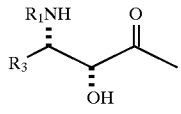
8. A process for preparing a taxoid of the following formula (I):



(I)

in which:

Z represents a radical of formula (II):



(II)

in which:

R_1 represents a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, and trifluoromethyl radicals,

a thenoyl radical,

a furoyl radical, or

a radical R_2—O—CO— in which R_2 represents:

an alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents selected from halogen atoms; hydroxyl radicals; alkoxy radicals containing 1 to 4 carbon atoms; dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms; piperidino radicals; morpholino radicals; 1-piperazinyl radicals optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms; cycloalkyl radicals containing 3 to 6 carbon atoms; cycloalkenyl radicals containing 4 to 6 carbon atoms; phenyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms; cyano radicals; carboxyl radicals; and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms; alkyl radicals containing 1 to 4 carbon atoms; and alkoxy radicals containing 1 to 4 carbon atoms,

a 5-membered aromatic heterocyclic radical, or

a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

R_3 represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or α- or β-naphthyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, or

a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

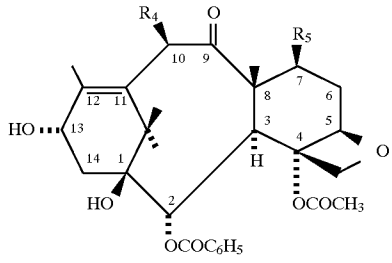
with the proviso that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals in the definitions of R_2 and R_3, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

R_4 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and

R_5 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

said process comprising:

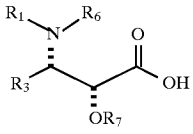
esterifying a product of formula (III):



(III)

in which R_4 and R_5 are defined as above

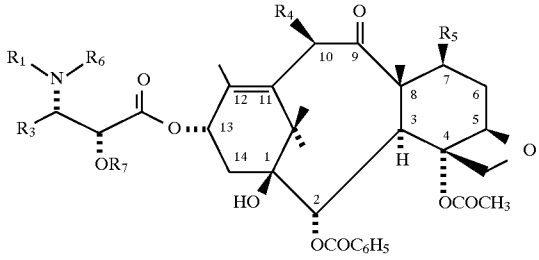
with an acid of formula (IV):



(IV)

in which R_1 and R_3 are defined as above, and either R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, or R_6 and R_7 together form a saturated 5- or 6-membered heterocycle, or

with a derivative of said acid, to obtain an ester of formula (V):

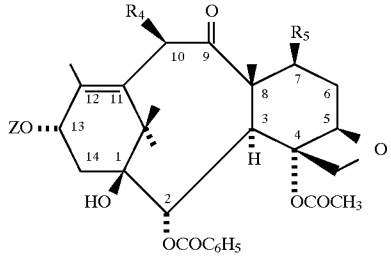


(V)

in which R_1, R_3, R_4, R_5, R_6 and R_7 are defined as above, and

replacing the protective group(s) of said ester of formula (V), represented by R_7 or R_6 and R_7 together, by hydrogen atoms.

9. A process for preparing a new taxoid of the following formula (I):



(I)

in which:

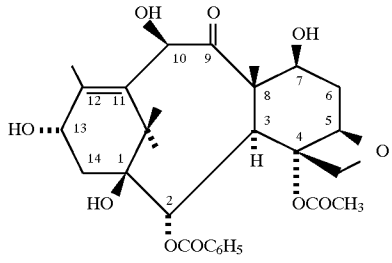
Z represents a hydrogen atom,

R_4 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and

R_5 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

said process comprising:

treating 10-deacetylbaccatin III of formula (IX):

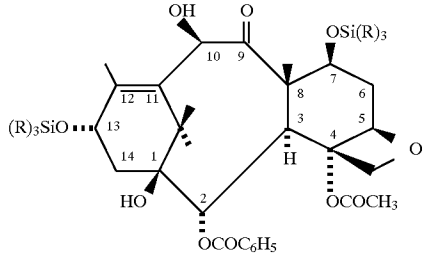


(IX)

with a silyl halide of formula:

$$(R)_3—Si—Hal \qquad (X)$$

in which the symbols R, which may be identical or different, represent an alkyl radical containing 1 to 6 carbon atoms, optionally substituted with a phenyl radical, a cycloalkyl radical containing 3 to 6 carbon atoms or a phenyl radical, to obtain a product of formula (XI):



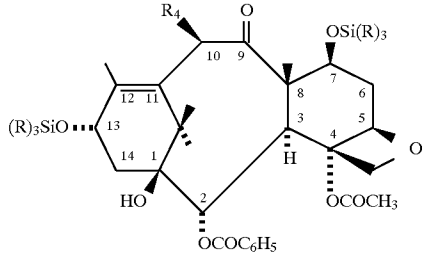
(XI)

in which R is defined as above,

treating said product of formula (XI) with a product of formula:

$$R'_4—X_1 \qquad (XII)$$

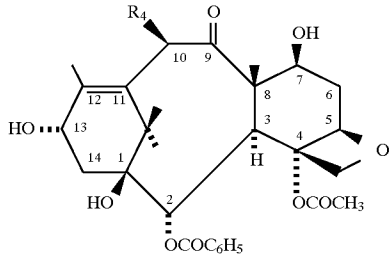
in which R'_4 represents a radical such that R'_4—O is identical to R_4 defined above and X_1 represents a halogen atom or a reactive ester residue, to obtain a product of formula (XIII):



(XIII)

in which R and R_4 are defined as above,

replacing the silyl protective groups of said product of formula (XIII) by hydrogen atoms to obtain a product of formula (XIV):



(XIV)

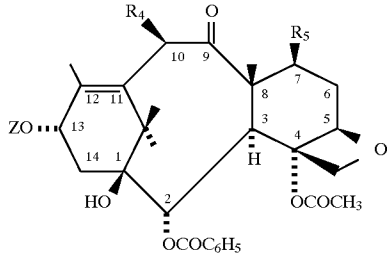
in which R_4 is defined as above, and

etherifying said compound of formula (XIV) selectively at position 7 with a product of formula (XV):

$$R'_5—X_2 \quad \text{(XV)}$$

in which R'_5 represents a radical such that R'_5—O is identical to R_5 defined as above and X_2 represents a reactive ester residue or a halogen atom, to give the product of formula (I) in which Z represents a hydrogen atom.

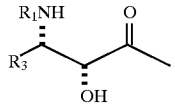
10. A process for preparing a taxoid of the following formula (I):



(I)

in which:

Z represents a radical of formula (II):



(II)

in which:

R_1 represents a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, and trifluoromethyl radicals,

a thenoyl radical,

a furoyl radical, or

a radical R_2—O—CO— in which R_2 represents:

an alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents selected from halogen atoms; hydroxyl radicals; alkoxy radicals containing 1 to 4 carbon atoms; dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms; piperidino radicals; morpholino radicals; 1-piperazinyl radicals optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms; cycloalkyl radicals containing 3 to 6 carbon atoms; cycloalkenyl radicals containing 4 to 6 carbon atoms; phenyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms; cyano radicals; carboxyl radicals; and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms; alkyl radicals containing 1 to 4 carbon atoms; and alkoxy radicals containing 1 to 4 carbon atoms,

a 5-membered aromatic heterocyclic radical, or

a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

R_3 represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or α- or β-naphthyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, or

a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

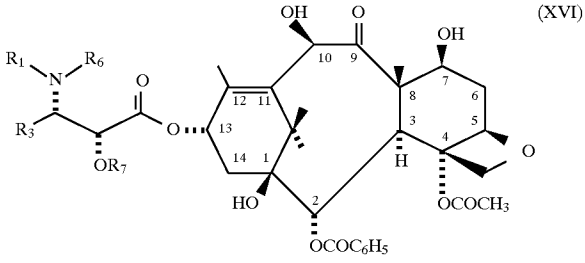
with the proviso that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals in the definitions of R_2 and R_3, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

R_4 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and

R_5 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

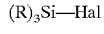
said process comprising:

treating a product of formula (XVI):



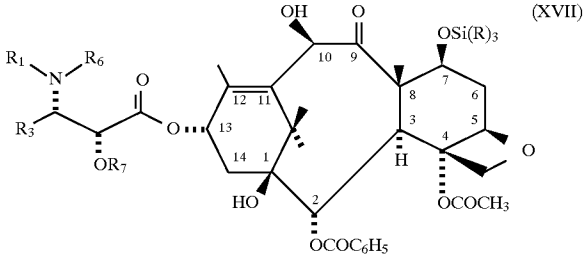
(XVI)

in which R_1, R_3, R_6 and R_7 are defined as above, with a product of formula (X):



(X)

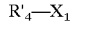
in which the symbols R, which may be identical or different, represent an alkyl radical containing 1 to 6 carbon atoms, optionally substituted with a phenyl radical, or a cycloalkyl radical containing 3 to 6 carbon atoms or a phenyl radical, to obtain a product of formula (XVII):



(XVII)

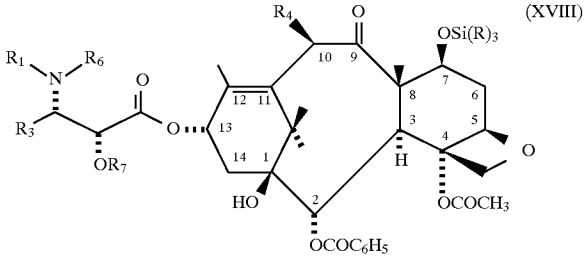
in which R, R_1, R_3, R_6 and R_7 are defined as above,

functionalizing said compound of formula (XVII) at position 10 with a product of formula:



(XII)

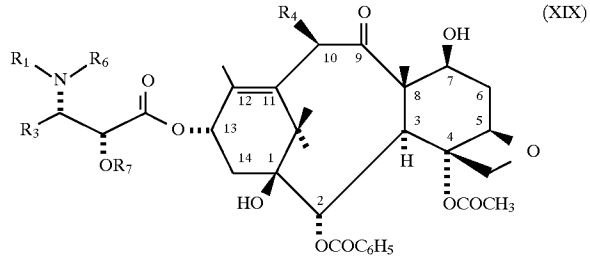
in which R'_4 represents a radical such that R'_4—O is identical to R_4 defined as above and X_1 represents a halogen atom or a reactive ester residue, to give a product of formula (XVIII):



(XVIII)

in which R, R_1, R_3, R_4, R_6 and R_7 are defined as above,

replacing the silyl protective group of said product of formula (XVIII) by a hydrogen atom to give a product of formula (XIX):



(XIX)

in which R_1, R_3, R_4, R_6 and R_7 are defined as above which, when reacted with a product of formula (XV):

(XV)

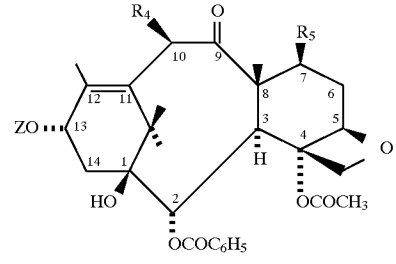
in which R'_5 represents a radical such that R'_5O is identical to R_5 defined above and X_2 represents a reactive ester residue or a halogen atom,

yields the product of formula (V):

(V)

in which R_1, R_3, R_4, R_5, R_6 and R_7 are defined as above and replacing the protective group(s) of formula (V) with one or two hydrogen atoms to give a product of formula (I) in which Z represents a radical of formula (II).

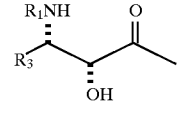
11. A process for preparing a taxoid of the following formula (I):



(I)

in which:

Z represents a hydrogen atom or a radical of formula (II):



(II)

in which:

R_1 represents a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, and trifluoromethyl radicals,

a thenoyl radical,

a furoyl radical, or

a radical R_2—O—CO— in which R_2 represents:

an alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an

alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents selected from halogen atoms; hydroxyl radicals; alkoxy radicals containing 1 to 4 carbon atoms; dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms; piperidino radicals; morpholino radicals; 1-piperazinyl radicals optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms; cycloalkyl radicals containing 3 to 6 carbon atoms; cycloalkenyl radicals containing 4 to 6 carbon atoms; phenyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms; cyano radicals; carboxyl radicals; and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms; alkyl radicals containing 1 to 4 carbon atoms; and alkoxy radicals containing 1 to 4 carbon atoms,

a 5-membered aromatic heterocyclic radical, or

a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

R_3 represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or α- or β-naphthyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, or

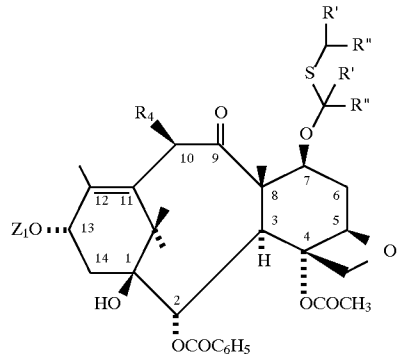
a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

with the proviso that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals in the definitions of R_2 and R_3, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

R_4 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and

R_5 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

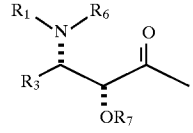
said process comprising reacting activated Raney nickel, in the presence of an aliphatic alcohol containing 1 to 3 carbon atoms or an ether, with a product of formula (XXI):



(XXI)

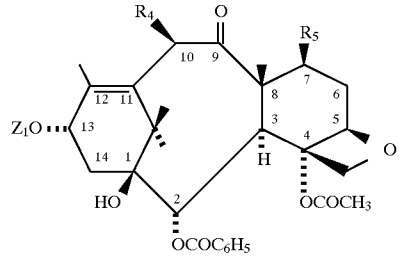
in which R_4 is defined as above, and R' and R", which may be identical or different,

represent a hydrogen atom or an alkyl radical containing 1 to 6 carbon atoms, an alkenyl radical containing 2 to 6 carbon atoms, an alkynyl radical containing 3 to 6 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms or a cycloalkenyl radical containing 3 to 6 carbon atoms, optionally substituted, or alternatively R' and R", together with the carbon atom to which they are linked, form a cycloalkyl radical containing 3 to 6 carbon atoms or a cycloalkenyl radical containing 4 to 6 carbon atoms, and Z_1 represents a hydrogen atom or a radical of formula (XXII):



(XXII)

in which R_1 and R_3 are defined as above and either R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, or R_6 and R_7 together form a saturated 5- or 6-membered heterocycle, to obtain a product of formula (XXIII):



(XXIII)

followed, when Z_1 represents a radical of formula (XXII), by replacing the protective group(s) represented by R_6 or R_6 and R_7 together by hydrogen atoms under the following conditions:

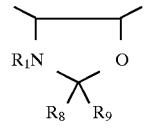
1) when R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, said replacing the protective groups by hydrogen atoms is accomplished

with at least one inorganic or organic acid in an organic solvent selected from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons and nitrites at a temperature from −10° to 60° C., or

with a source of fluoride ions, or

with catalytic hydrogenation, or

2) when R_6 and R_7 together form a saturated 5- or 6-membered heterocycle of formula (VI):



(VI)

in which R_1 is defined as above and R_8 and R_9, which may be identical or different,

represent a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, or an aralkyl radical in which the alkyl portion contains 1 to 4 carbon atoms, or an aryl radical, or

alternatively R_8 represents an alkoxy radical containing 1 to 4 carbon atoms or a trihalomethyl radical or a phenyl radical substituted with a trihalomethyl radical and R_9 represents a hydrogen atom, or

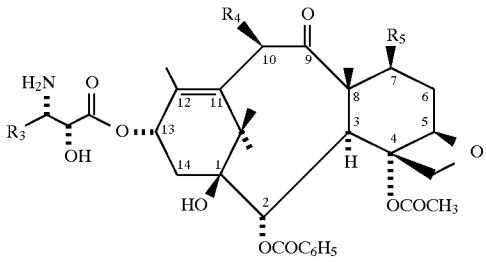
alternatively R_8 and R_9, together with the carbon atom to which they are linked, form a 4- to 7-membered ring, and further wherein when:

a) R_1 represents a tert-butoxycarbonyl radical and R_8 and R_9, which may be identical or different, represent an alkyl radical or an aralkyl or aryl radical, or

alternatively R_8 represents a trihalomethyl radical or a phenyl radical substituted with a trihalomethyl radical and R_9 represents a hydrogen atom, or

alternatively R_8 and R_9 together form a 4- to 7-membered ring, said replacing the protective groups by hydrogen atoms is accomplished

by treating the ester of formula (V) with an inorganic or organic acid, and optionally, with an organic solvent, to obtain the product of formula (VII):



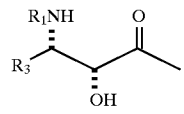
(VII)

in which R_3, R_4 and R_5 are defined as in claim **1**, and acylating said product of formula (VII) with benzoyl chloride in which the phenyl ring is optionally substituted; thenoyl chloride; furoyl chloride; or a product of formula (VIII):

$$R_2—O—CO—X \qquad \text{(VII)}$$

in which R_2 is defined as above and X represents a halogen atom or a residue —O—R_2 or —O—CO—O—R_2,

to obtain a product of formula (I) in which Z represents a radical of formula (II),



(II)

or

b) R_1 represents an optionally substituted benzoyl radical, a thenoyl or furoyl radical or a radical $R_2O—CO—$ in which R_2 is defined as above, R_8 represents a hydrogen atom or an alkoxy radical containing 1 to 4 carbon atoms or a phenyl radical substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms and R_9 represents a hydrogen atom,

said replacing of the protective group formed by R_6 and R_7 together by two hydrogen atoms is accomplished

in the presence of at least one inorganic or organic acid in a stoichiometric or catalytic amount, and in an organic solvent selected from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons and aromatic hydrocarbons

at a temperature of from −10° to 60° C.

12. A process according to claim **8**, wherein said esterifying step is performed with an acid of formula (IV) in the presence of a condensing agent and an activating agent in an organic solvent at a temperature of from −10° to 90° C.

13. A process according to claim **8**, wherein said esterifying step is performed with an acid of formula (IV) in the form of the symmetrical anhydride thereof, in the presence of an activating agent in an organic solvent at a temperature of from 0° to 90° C.

14. A process according to claim **8**, wherein said esterifying step is performed with the acid of formula (IV) in halide form or in the form of a mixed anhydride with an aliphatic or aromatic acid, optionally prepared in situ, in the presence of a base, in an organic solvent at a temperature of from 0° to 80° C.

15. A process according to claim **8**, further comprising replacing the protective group(s) R_7 or R_6 and R_7 together by hydrogen atoms, wherein:

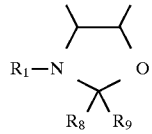
1) when R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, said replacing the protective groups by hydrogen atoms is accomplished

with at least one inorganic or organic acid in an organic solvent selected from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons and nitrites at a temperature from −10° to 60° C., or

with a source of fluoride ions, or

with catalytic hydrogenation,

2) when R_6 and R_7 together form a saturated 5- or 6-membered heterocycle of formula (VI).



(VI)

in which R^1 is defined as in claim **8** and R_8 and R_9, which may be identical or different,

represent a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, or an aralkyl radical in which the alkyl portion contains 1 to 4 carbon atoms, or an aryl radical, or

alternatively R_8 represents an alkoxy radical containing 1 to 4 carbon atoms or a trihalomethyl radical or a phenyl radical substituted with a trihalomethyl radical and R_9 represents a hydrogen atom, or

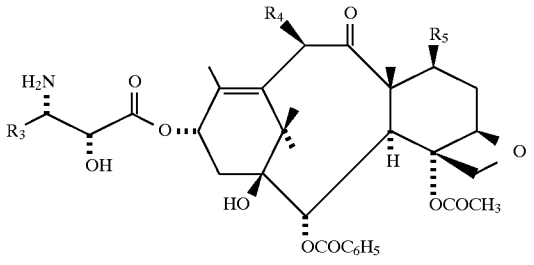
alternatively R_8 and R_9 together with the carbon atom to which they are linked, form a 4- to 7-membered ring, and further wherein when:

a) R_1 represents a tert-butoxycarbonyl radical and R_8 and R_9 which may be identical or different, represent an alkyl radical or an aralkyl or aryl radical, or

alternatively R_6 represents a trihalomethyl radical or a phenyl radical substituted with a trihalomethyl radical and R_9 represents a hydrogen atom, or

alternatively R_8 and R_9 together form a 4- to 7-membered ring,

the ester of formula (V) is treated with an inorganic or organic acid, and optionally, in an organic solvent, to obtain the product of formula (VII):



(VII)

in which

R_3, R_4 and R_5 are defined in claim **8**, and

said product of formula (VII) is acylated with benzoyl chloride in which the phenyl ring is optionally substituted or thenoyl chloride, or furoyl chloride or a product of formula (VIII):

$$R_2—O—CO—X \quad \text{(VIII)}$$

in which R_2 is defined in claim **8** and X represents a halogen atom or a residue —O—R_2 or —O—CO—O—R_2, to obtain a product of formula (I) in which Z represents a radical of formula (II),

b) when R_1 represents an optionally substituted benzoyl radical, a thenoyl or furoyl radical or a radical R_2O—CO— in which R_2 is defined as above, R_6 represents a hydrogen atom or an alkoxy radical containing 1 to 4 carbon atoms or a phenyl radical substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms and R_9 represents a hydrogen atom,

the protective group formed by R_6 and R_7 is replaced by hydrogen atoms in the presence of at least one inorganic or organic acid in a stoichiometric or catalytic amount, and in an organic solvent selected from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons and aromatic hydrocarbons at a temperature of from −10° to 60° C.

16. A process according to claim **15**, wherein when R_6 and R_7 together form a saturated 5- or 6-membered heterocycle of formula (VI), and R_8 and R_9 which may be identical or different, represent an aralkyl radical in which the alkyl portion contains 1 to 4 carbon atoms, the aryl portion of said aralkyl radical represents a phenyl radical optionally substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms.

17. A process according to claim **15**, wherein when R_6 and R_7 together form a saturated 5- or 6-membered heterocycle of formula (VI), and R_8 and R_9, which may be identical or different, represent an aryl radical, said aryl radical is a phenyl radical optionally substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms.

18. A process according to claim **15**, wherein said temperature ranges from 15° to 30° C.

19. A process according to claim **15**, wherein said source of fluoride ions is a hydrofluoric acid/triethylamine complex.

20. A process according to claim **15**, wherein said trihalomethyl radical is trichloromethyl.

21. A process according to claim **15**, wherein when said ester of formula (V) is treated in an organic solvent, said organic solvent is an alcohol.

22. A process according to claim **7**, wherein said activated Raney nickel is present in step (b) in an ethanolic suspension and further wherein said acid in step (c) is an ethanolic solution of hydrochloric acid.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,847,170
DATED : Dec. 8, 1998
INVENTOR(S) : Herve Bouchard, et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 4, Column 29, Line 42, after "chain", delete " , ";

Claim 4, Column 30, Line 63, after "chain", insert --and--;

Claim 4, Column 31, Lines 3-12, to the upper right of the formula, insert --(v)--;

Claim 5, Column 31, Lines 20-29, to the upper right of the formula, insert --(V)--;

Claim 8, Column 33, Line 34, "(1)" should read --(I);

Claim 11, Column 42, Line 66, "nitrites" should read --nitriles--;

Claim 15, Column 44, Line 39, "nitrites" should read --nitriles--;

Claim 15, Column 44, Line 44, "(VI)." should read --(VI):--;

Claim 15, Column 44, Line 66, after "R_9", insert --,--;

Claim 15, Column 45, Line 21, after "defined", insert --as--; and

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,847,170 Page 2 of 2

DATED : Dec. 8, 1998

INVENTOR(S) : Herve Bouchard, et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 15, Column 45, Line 34, "R6" should read --R_8--.

Signed and Sealed this

Seventh Day of September, 1999

Attest:

Q. TODD DICKINSON

Attesting Officer

Acting Commissioner of Patents and Trademarks

EXHIBIT B

US007241907B2

(12) **United States Patent**
Didier et al.

(10) **Patent No.: US 7,241,907 B2**
(45) **Date of Patent: Jul. 10, 2007**

(54) **ACETONE SOLVATE OF DIMETHOXY DOCETAXEL AND ITS PROCESS OF PREPARATION**

(75) Inventors: **Eric Didier**, Paris (FR); **Marc-Antoine Perrin**, Jouy en Josas (FR)

(73) Assignee: **Aventis Pharma S.A.**, Antony (FR)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 449 days.

(21) Appl. No.: **10/944,254**

(22) Filed: **Sep. 17, 2004**

(65) **Prior Publication Data**

US 2005/0065138 A1 Mar. 24, 2005

Related U.S. Application Data

(60) Provisional application No. 60/519,895, filed on Nov. 14, 2003.

(30) **Foreign Application Priority Data**

Sep. 19, 2003 (FR) 03 11016

(51) **Int. Cl.**
C07D 305/00 (2006.01)
C07D 407/00 (2006.01)
C07D 493/00 (2006.01)

(52) **U.S. Cl.** **549/510**

(58) **Field of Classification Search** 549/510
See application file for complete search history.

(56) **References Cited**

FOREIGN PATENT DOCUMENTS

EP	0982027	* 3/2000
WO	WO 96/30355	* 10/1996
WO	WO 97/32869	* 9/1997

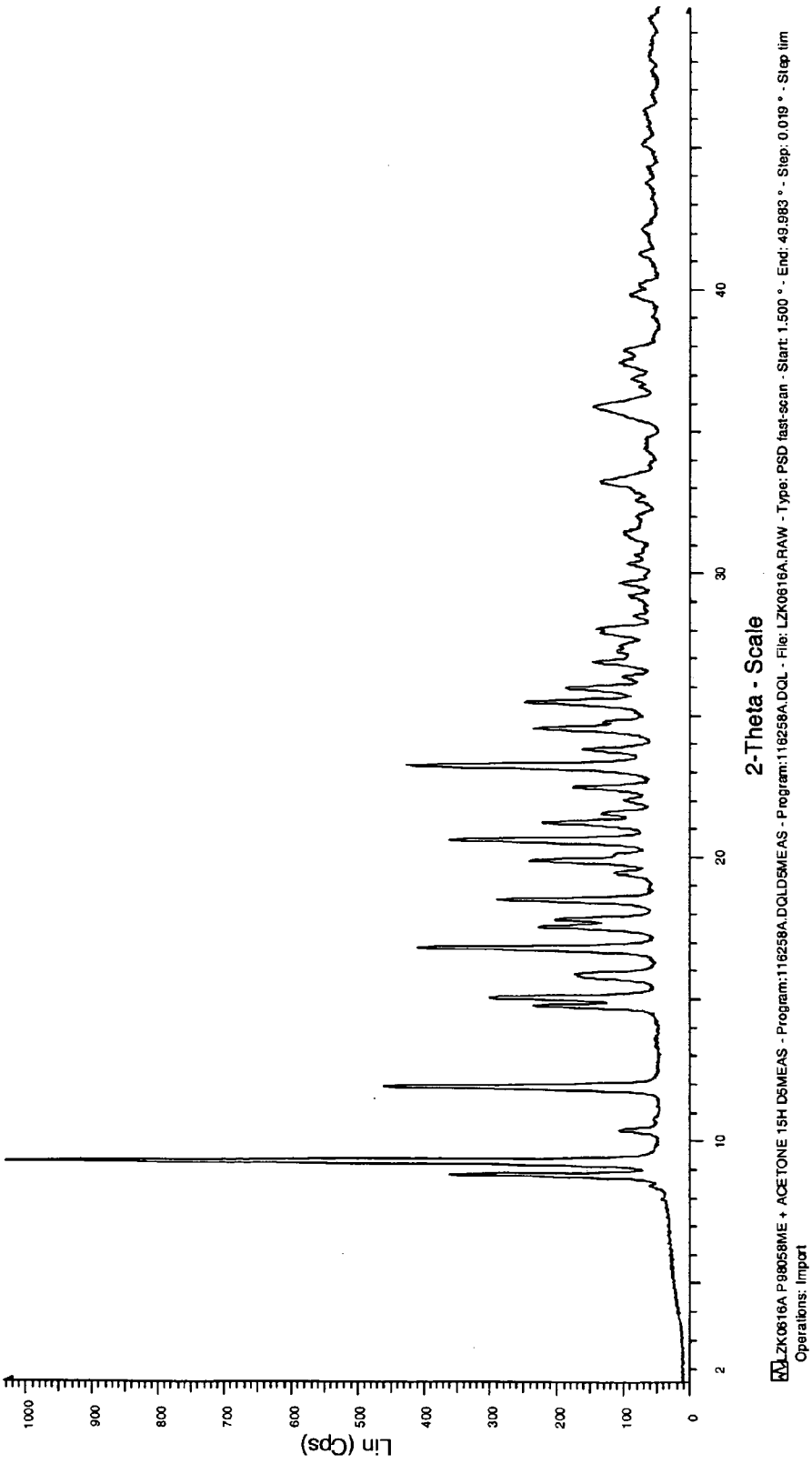
* cited by examiner

Primary Examiner—Margaret D. Seaman
Assistant Examiner—Niloofar Rahmani
(74) *Attorney, Agent, or Firm*—Balaram Gupta; Paul R. Darkes

(57) **ABSTRACT**

This invention discloses and claims an acetone solvate of dimethoxydocetaxel or 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1-hydroxy-7β,10β-dimethoxy-9-oxotax-11-en-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate and its preparation by crystallization from an aqueous/acetone solution.

16 Claims, 1 Drawing Sheet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800
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2
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2-Theta - Scale
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Operations: Import

FIG. 1

ACETONE SOLVATE OF DIMETHOXY DOCETAXEL AND ITS PROCESS OF PREPARATION

This application claims the benefit of U.S. Provisional Application No. 60/519,895, filed Nov. 14, 2003 and benefit of priority of French Patent Application No. 03/11,016, filed Sep. 19, 2003, both of which are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to the acetone solvate of dimethoxydocetaxel or 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1-hydroxy-7β,10β-dimethoxy-9-oxotax-11-en-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate and to its process of preparation.

2. Description of the Art

4-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1-hydroxy-7β,10β-dimethoxy-9-oxotax-11-en-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate exhibits noteworthy anticancer and antileukemic properties.

4-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1-hydroxy-7β,10β-dimethoxy-9-oxotax-11-en-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate is prepared according to the process which is disclosed more particularly in international application PCT WO 96/30355 or international application PCT WO 99/25704; according to the process disclosed in these applications, the product is not crystallized and is not characterized.

All of the references described herein are incorporated herein by reference in their entirety.

SUMMARY OF THE INVENTION

It has been found that the acetone solvate of 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1-hydroxy-7β,10β-dimethoxy-9-oxotax-11-en-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate is fully characterized from a chemical viewpoint.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a powder x-ray diffraction (PXRD) diagram of the acetone solvate form of the product of Example 1.

DETAILED DESCRIPTION OF THE INVENTION

According to the invention, the acetone solvate of 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1-hydroxy-7β,10β-dimethoxy-9-oxotax-11-en-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate can be obtained by crystallization of 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1-hydroxy-7β,10β-dimethoxy-9-oxotax-11-en-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate from a mixture of water and of acetone, followed by drying the isolated product under reduced pressure.

For the implementation of the process according to the invention, it can be particularly advantageous

to dissolve 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1-hydroxy-7β,10β-dimethoxy-9-oxotax-11-en-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate in acetone,

to treat the solution with water,

to seed the solution with a suspension of said product in an acetone/water mixture and then to again treat with water,

to separate the crystals obtained, then

to dry them under reduced pressure.

Generally, 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1-hydroxy-7β,10β-dimethoxy-9-oxotax-11-en-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate is dissolved in acetone. Preferably, the amount of acetone is between 5 and 20 parts by volume (ml) with respect to the weight (in grams) of 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1-hydroxy-7β,10β-dimethoxy-9-oxotax-11-en-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate employed (ideally 10).

The preferred seeding is carried out at a concentration of 60 to 80 g (ideally 68 g) per liter of mixture comprising an acetone/water ratio by volume of from about 65/35 to about 75/25 and preferably of approximately about 68/32. The acetone/water mixture by volume at the end of precipitation is between 70/30 minimum and 30/70 maximum (ideally 45/55). The entire crystallization process takes place, according to a better way of implementing the invention, at 20±5° C. (ideally 20° C.).

The acetone solvate of 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1-hydroxy-7β,10β-dimethoxy-9-oxotax-11-en-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate which crystallizes is separated, preferably by filtration or centrifuging. Drying is carried out under a reduced pressure generally of between 0.5 and 30 kPa, preferably in the region of 0.7 kPa, at a temperature of between 30 and 60° C., preferably in the region of 40° C.

The drying of the product was studied. Thus, samples of acetone solvate of 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1-hydroxy-7β,10β-dimethoxy-9-oxotax-11-en-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate deliberately treated at a temperature above 70° C. (70 to 100° C.) shows an increasing loss in the content of acetone with the increase in the temperature. For the drying, the preferred temperature is thus between 30 and 60° C. and more preferably still is in the region of 40° C. A mean value of the content of acetone is 7%, which represents approximately the acetone stoichiometry, which is 6.5%, for a solvate comprising one molecule of acetone.

The present invention will be more fully described using the following examples, which should not be regarded as limiting the invention.

EXAMPLE 1

940 ml of purified water are added at 20±5° C. ambient temperature to a solution of 207 g of approximately 92% by weight 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1-hydroxy-7β,10β-dimethoxy-9-oxotax-11-en-13α-yl in approximately 2 liters of acetone and then seeding is carried out with a suspension of 2 g of 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1-hydroxy-7β,10β-dimethoxy-9-oxotax-11-en-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate, isolated from acetone/water, in a mixture of 20 ml of water and 20 ml of acetone. The mixture is left stirring for approximately 10 to 22 hours and 1.5 liters of purified water are added over 4 to 5 hours. The mixture is left stirring for 60 to 90 minutes and then the suspension is filtered under reduced pressure. The cake is washed on the filter with a solution prepared from 450 ml of acetone and 550 ml of purified water and is then dried in an oven at 55° C. under reduced pressure (0.7 kPa) for 4 hours. 197 g of 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1-hydroxy-7β,10β-dimethoxy-9-oxotax-11-en-13α-yl (2R,3S)-3-tert-butoxy-

carbonylamino-2-hydroxy-3-phenyl-propionate.acetone, comprising 0.1% of water and 7.2% of acetone (theoretically 6.5% for a stoichiometric solvate), are obtained.

Drying Study

The product is again placed in an oven and successively dried for 18 hours at 60° C. under a reduced pressure of 0.7 kPa, for 3 hours at 60° C. under a relative humidity of approximately 80% (reduced pressure of 160 mmHg) and for 18 hours at 70° C. under a relative humidity of approximately 80% (reduced pressure of 200 mmHg). At this stage, the content of water is 0.2% and the content of acetone is 4.7% (194 g). At this same stage, 1 aliquot of 1 g of the batch is dried under a reduced pressure of 5 mmHg successively for 18 hours at 80° C. (residual acetone content of 0.5%) and then for 21 hours at 100° C. (residual acetone content of 0.02%). The remainder is dried at 80° C. under a reduced pressure of 5 mmHg for 31 hours (acetone 1.7%, water 0.3%, assay with regard to such of 96.5%, purity of greater than 99%).

Operating Conditions Used for the Acquisition of the PXRD Diagram (FIG. **1**)

The analyses are carried out on the Bruker D5000 diffractometer equipped with an Anton Paar TTK temperature chamber. The set-up in reflection possesses focusing geometry of Bragg-Brentano type (θ—θ). The powder is deposited on a hollow aluminum sample holder. A cobalt anticathode tube (40 kV/30 mA) supplies iron-filtered incident radiation. Radiation is emitted at two wavelengths: Co $K\alpha_1$ (λ=1.7890 Å) and Co $K\alpha_2$ (λ=1.7929 Å). Filtering by iron does not completely remove the Kβ radiation (λ=1.6208 Å for cobalt), which still participates in the incident radiation at a level of 1% (manufacturer's data) of the intensity of the Kα doublet.

Soller slits improve the parallelism of the beam. Variable front slits make it possible to retain a constant illumination area of the sample. A 1 mm collimator limits the scattering between the tube and the measuring chamber. A Braun 50 M multichannel linear detector is used. It exhibits a detection window with a width of 10° of 2θ angle. The conditions for recording the diagrams are as follows: scanning from 1.5 to 50° in 2θ, counting time of 30 seconds per degree in 2θ, under ambient conditions of temperature, pressure and relative humidity.

FIG. **1** represents the reference PXRD diagram of the solvate form comprising acetone (form A) of the product of example 1.

NMR Spectrum of the Product of Example 1

^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ in ppm): 1.20 (s, 3H), 1.22 (s, 3H), 1.37 (s, 9H), 1.67 (s, 1H), 1.72 (s, 3H), 1.80 (mt, 1H), 1.88 (s, 3H), 2.17 (s, 6H), from 2.20 to 2.40 (mt, 2H), 2.36 (s, 3H), 2.70 (mt, 1H), 3.30 (s, 3H), 3.46 (s, 3H), 3.47 (mt, 1H), 3.82 (d, J=7.5 Hz, 1H), 3.86 (dd, J=11 and 6.5 Hz, 1H), 4.17 (d, J=8.5 Hz, 1H), 4.30 (d,J=8.5 Hz, 1H), 4.63 (mt, 1H), 4.80 (s, 1H), 4.97 (broad d, J=10 Hz, 1H), 5.27 (broad d, J=10 Hz, 1H), 5.44 (d, J=10 Hz, 1H), 5.64 (d, J=7.5 Hz, 1H), 6.21 (t, J=9 Hz, 1H), from 7.25 to 7.45 (mt, 5H), 7.49 (t, J=7.5 Hz, 2H), 7.60 (broad t, J=7.5 Hz, 1H), 8.09 (d, J=7.5 Hz, 2H).

What is claimed is:

1. An acetone solvate of 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1-hydroxy-7β,10β-dimethoxy-9-oxotax-11-en-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

2. An acetone solvate of 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1-hydroxy-7β,10β-dimethoxy-9-oxotax-11-en-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate comprising from about 5 to about 7 percent by weight of acetone.

3. A process for the preparation of the acetone solvate of 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1-hydroxy-7β,10β-dimethoxy-9-oxotax-11-en-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate, which comprises:

crystallizing 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1-hydroxy-7β,10β-dimethoxy-9-oxotax-11-en-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate from a mixture of water and acetone, which comprises seeding the solution with a suspension of said product in an acetone/water mixture and then subsequently treating with water, and which comprises drying the product obtained under reduced pressure.

4. The process as set forth in claim **3**, wherein the seeding is carried out at a concentration of from about 60 to about 80 g per liter of a mixture comprising an acetone/water ratio by volume of from about 65/35 to about 75/25.

5. The process as set forth in claim **4**, wherein the seeding is carried out in a mixture comprising an acetone/water ratio by volume of about 68/32.

6. The process as set forth in claim **3**, wherein the acetone/water mixture by volume at the end of precipitation is from about 70/30 to about 30/70.

7. The process as set forth in claim **6**, wherein the acetone/water mixture by volume at the end of precipitation is about 45/55.

8. The process as set forth in claim **3**, wherein the crystallization process takes place at about 20±5° C.

9. The process as set forth in claim **4**, wherein the crystallization process takes place at about 20±5° C.

10. The process as set forth in claim **5**, wherein the crystallization process takes place at about 20±5° C.

11. The process as set forth in claim **6**, wherein the crystallization process takes place at about 20±5° C.

12. The process as set forth in claim **7**, wherein the crystallization process takes place at about 20±5° C.

13. The process as set forth in claim **3**, wherein drying is carried out at a temperature in the range of from about 30 and about 60° C.

14. The process as set forth in claim **13**, wherein drying is further carried out under a pressure in the region of 0.7 kPa.

15. The process as set forth in claim **3**, wherein drying is carried out at a temperature of about 40° C. under a pressure in the region of 0.7 kPa.

16. The process as set forth in claim **3**, wherein the preparation is carried out directly starting from the acetone solution of 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1-hydroxy-7β,10β-dimethoxy-9-oxotax-11-en-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate obtained by deprotection in an acid medium of the ester 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1-hydroxy-7β,10β-dimethoxy-9-oxotax-11-en-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyloxazolidine-5-carboxylate.

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